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The Development of a Practical and Reliable Large-Scale Synthesis of 2,6-Diamino-4-bromopyridine

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Abstract:

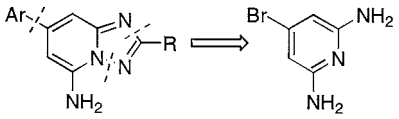
A novel, safer, and efficient synthetic route to 2,6-diamino-4-bromopyridine has been developed. In discovery research a five-step synthesis afforded 2,6-diamino-4-bromopyridine in 56% yield with a double Curtius rearrangement as a key transformation. Due to potential safety concerns on larger scale an alternative synthetic strategy was necessary. Starting from 2,4-dibromopyridine-*N*-oxide two complementary procedures have been developed to access 2,6-diamino-4-bromopyridine. The four-step procedure yielded in 28% overall, and the five-step procedure, in 33% overall 2,6-diamino-4-bromopyridine in a safe and straightforward manner using a regioselective 2,6-diamination reaction as key step. Additionally, a general route to unsymmetrical substituted pyridine *N*-oxide derivatives is disclosed.

The Medicinal Chemistry Synthesis

In the course of a medicinal chemistry program leading to [1,2,4]-triazolo-[1,5-*a*]-pyridine derivatives[1] **1** the retrosynthetic analysis identified 2,6-diamino-4-bromopyridine **2** as the key intermediate for the desired route (Scheme 1).

Chelidamic acid[2] **3** was identified as a suitable starting material for the synthesis of 2,6-diamino-4-brompyridine **2** and displays the desirable 2,4,6-trisubstitution pattern. **3** was previously described to be efficiently converted to the 4-brominated diethyl ester **4**.[3] In our hands the synthesis of **4** proved to be straightforward in this manner and was used to prepare multigram quantities in good yields. Closer examination showed the reaction to be potentially hazardous due to the use of excess PBr_5 in CCl_4 at reflux temperature and to the intermediacy of the bis-carbonylbromide which reacted exothermically with ethanol to form the bis-ester **4**. Consequently, the conversion had to be carefully monitored. Conversion of the bis-ester **4** to the bis-hydrazide **5** was achieved by heating a mixture of the bis-ester **4** with hydrazine hydrate in ethanol for 1 h at 80 °C. Upon cooling of the reaction mixture to ambient temperature the desired bis-hydrazide **5** precipitated from the solution in 90% yield as a white amorphous solid. The product proved to be analytically pure after filtration, washing, and drying. The double Curtius rearrangement[4] was a key step in the synthesis of 2,6-diamino-4-bromopyridine **2**, and careful diazotization of the bis-hydrazide **5** with $NaNO_2$ resulted in formation of the bis-acyl azide **6**. Addition of aqueous sodium bicarbonate to the reaction mixture led to precipitation of **6** which was filtered off and washed thoroughly with water to remove accompanying salt remains. Several attempts to successfully perform the double Curtius rearrangement under aqueous conditions failed to yield satisfactory amounts of the bis-amine **2**. In addition heating a sample of the wet precipitate of bis-acyl-azide **6** in *tert*-butyl alcohol to quench the bis-isocyanate intermediate and form the bis-Boc derivative **7** proved to be only of limited success. Due to these observations we assumed that water formed adverse side products, thus considerably limiting the chemical yields. Therefore, water was removed from **6** by dissolution of the wet precipitate in either chloroform or dichloromethane and treatment of the solution with $MgSO_4$. Removal of $MgSO_4$ by filtration and evaporation of the organic solvent at temperatures below 10 °C under reduced pressure yielded in 90% intermediate **6** which was pure enough[5] to be subjected to the double Curtius rearrangement. In the event, the bis-acyl azide was heated under reflux in *tert*-butyl alcohol for 12 h. After removal of excess *tert*-butyl alcohol, the crude bis-Boc derivative **7**[6] was treated with TFA in DCM to obtain the desired 2,6-diamino-4-bromopyridine **2** in 74% yield from bis-acyl azide **6**. This reaction sequence was also scalable to yield multigram quantities of **2** without

Scheme 1. **Retrosynthetic analysis of 1**



1 **2**

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(5) Purity of **6** was determined by reversed phase analytical HPLC at 230 nm. Purity was generally higher than 90%.

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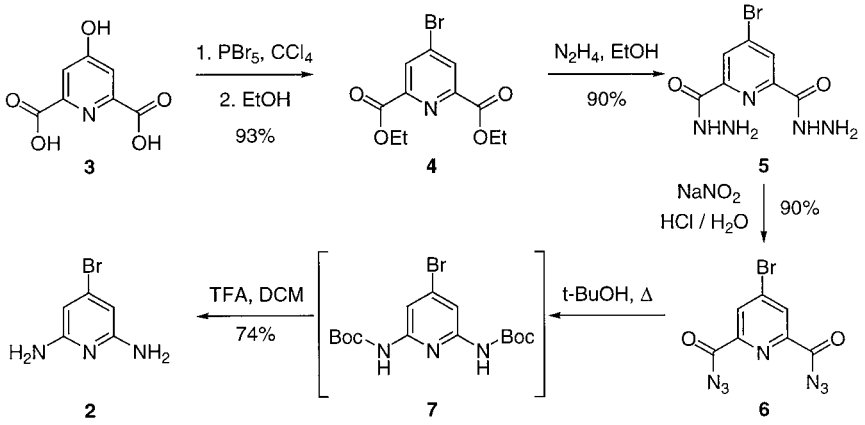
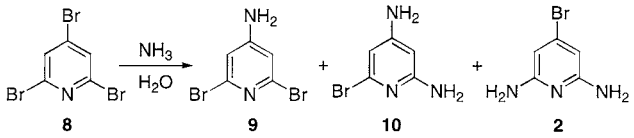
Scheme 2. **Research synthesis of 2,6-diamino-4-bromopyridine 2**



Scheme 3. **Ammonolysis of 2,4,6-tribromopyridine 8**



observation of spontaneous decomposition of bis-acyl azide **6** (Scheme 2).

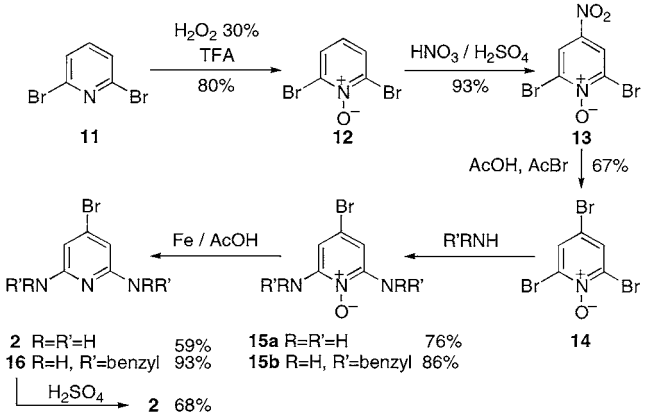
However, a serious limitation to this route was clearly seen in the ubiquitous uncertainty regarding the potential for spontaneous decomposition of bis-acyl azide **6** in a dry state. We never observed any spontaneous extrusion of nitrogen at this stage, but an azide-free route would be preferred, and an alternative route towards 2,6-diamino-4-brompyridine **2**, easily amenable to large-scale synthesis, was highly desirable.

The Kilogram Laboratory Synthesis

To avoid potential safety risks by scaling up the medicinal chemistry route towards 2,6-diamino-4-bromopyridine **2** the well-known ammonolysis of 2,4,6-tribromopyridine **8**[7] was considered as a possible alternative.[8] Upon reaction of 2,4,6-tribromopyridine **8** with aqueous ammonia the starting material was converted into an almost inseparable mixture of products consisting of 4-amino-2,6-dibromopyridine **9**, 2,4-diamino-6-bromopyridine **10**, and 2,6-diamino-4-bromopyridine **2** (Scheme 3).

On small scale (1−5 g) the desired 2,6-diamino-4-bromopyridine **2** was yielded approximately in 25%, whereas on larger scale (up to 100 g) the yield was significantly reduced (5%), thus making this direct approach not amenable to large-scale production. An alternative route employing pyridine *N*-oxides was then investigated.[9] 2,6-Dibromopyridine **11** is commercially available as a bulk chemical and

Scheme 4. **Scalable synthesis of 2,6-diamino-4-bromopyridine 2**



can serve here as a cheap starting material in the synthetic sequence. 2,6-Dibromopyridine-*N*-oxide **12**, which is also commercially available but more expensive, was easily accessible through *N*-oxidation with peroxide under acidic conditions. In a two-step procedure 2,4,6-tribromopyridinium-*N*-oxide **14** was conveniently prepared with 62% overall yield from **12**, according to literature procedures.[7,10] By using 2,4,6-tribromopyridinium-*N*-oxide **14** as starting material for the planned sequence, pleasingly the substitution reaction with ammonia as nucleophile occurred selectively at positions 2 and 6 without affecting position 4, yielding 2,6-diamino-4-bromopyridine-*N*-oxide **15a** in 76% (Scheme 4). Moreover, this reaction sequence was also possible for benzylamine, affording **15b** in 86% yield. The resulting *N*-oxides **15** were conveniently reduced with iron in acetic acid to the pyridine derivative **2** in 59% yield and the 2,6-dibenzylamine derivative **16** in 93% yield, respectively. Debenzylation of **16**, and thereby conversion to the desired 2,6-diamino-4-bromopyridine **2**, by catalytic hydrogenation failed because the debromination occurred first. The 2,4-dimethoxybenzyl group, more labile towards hydrogenation, proved a limited success since again the aryl bromide was predominantly reduced. However, treatment of **16** with 95% sulfuric acid at 40 °C afforded the desired product **2** in 68% yield (Scheme 4).[11]

(6) A small sample of intermediate **7** was purified by preparative HPLC on reversed phase eluting with an acetonitrile/water gradient, and the spectroscopic data are in accordance with the proposed structure. (4-Bromo-6-*tert*-butoxycarbonylaminopyridin-2-yl)-carbamic acid *tert*-butyl ester (**7**). Anal. Calcd for $C_{15}H_{22}BrN_3O_4$: C, 46.40; H, 5.71; N, 10.82; Br, 20.58. Found: C, 46.44; H, 5.62; N, 11.06; Br, 20.67. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.52 (s, 18H, CH_3), 7.20 (s, br, 2H, NH), 7.80 (s, 2H, H3,5). Mp 175.5 °C.

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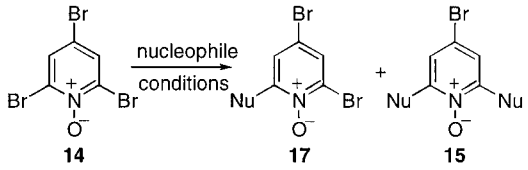
Scheme 5. **Nucleophilic mono- and disubstitution of 2,4,6-tribromopyridine-*N*-oxide 14**



This two-step protocol yielded the desired 2,6-diamino-4-bromopyridine **2** in 45% yield via ammonolysis of 2,4,6-tribromopyridinium-*N*-oxide **14** and subsequent reduction of the intermediate **15a** with iron in acetic acid. Alternatively, the three-step protocol via 2,6-dibenzylamino-4-bromopyridine-*N*-oxide **15b**, reduction of the *N*-oxide and cleavage of both benzyl groups, liberated in 54% overall yield the free bis-amine **2**. Both of the successful protocols are amenable to large-scale synthesis, thus offering a safe approach to 2,6-diamino-4-bromopyridine **2**. This constitutes an alternative approach towards 2,6-diamino-4-bromopyridine **2** with overall yields of 28% for the four-step or 33% for the five-step sequence from commercially available 2,6-dibromopyridine-*N*-oxide **12**.

A New Route to Unsymmetrical Substituted Pyridine Derivatives. During the preparation of the *N*-oxides **15** substantial amounts of monosubstituted product were identified by TLC and HPLC. The amount of monosubstitution varied, depending on reaction time, and temperature and prolonged heating at elevated temperatures resulted in complete disubstitution (Scheme 5). Monosubstituted products are obtained by running the reaction for shorter times at lower temperatures with lower concentrations of the nucleophile (entries 3, 5, 7, 8, 11), yielding the respective *N*-oxides in yields from 53 to 77%. It should be noted that sterically demanding primary amines (entries 8, 9) gave reliably good results. Preliminary results show that secondary amines (entry 12) afforded lower yields of products. Disubstitution can be achieved by employing higher temperatures, longer time periods, and increased amounts of nucleophiles (entries 1, 2, 4, 6, 10) in yields up to 86%. Thionucleophiles (entries 13, 14) only provide access to disubstituted products (Table 1).

Preliminary results directed towards the unsymmetrical substitution of pyridine-*N*-oxides with the method described above revealed a promising access to such compounds (Scheme 6). Monosubstituted products such as **17** undergo a second substitution with a different nucleophile easily. Reacting monobenzyl derivative **17b** with *N*-butylamine led to *N*-benzyl-4-bromo-*N*′-butyl-1-oxypyridine-2,6-diamine **18** in 48% yield. This procedure opens a general approach to unsymmetrical substituted pyridine derivatives.

Conclusions

In the course of a medicinal chemistry program we developed a new synthetic access to previously unknown 2,6-diamino-4-bromopyridine **2** in five steps in 56% overall yield with a double-Curtius rearrangement as a key step.

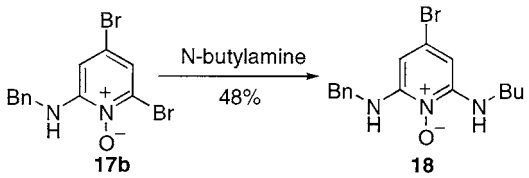
(11) (a) Kowalski P.; Majaka Z.; Kowalska T. *Chem. Heterocycl. Comput.* **1998**, *34*, 740−741.

Table 1. **Reaction of 2,4,6-Tribromopyridinium-*N*-oxide 14 with Nucleophiles**

			conditions		yield (%)	
entry	nucleophile	equiv	*t* (h)	*T* (°C)	**17**	**15**
1	a: NH_3 (aq)	50	3	100	13	60[a]
2	a: NH_3 (aq)	50	3.5	140	−	76[b]
3	b: benzylamine	6	2	70	73[a]	12[a]
4	b: benzylamine	100	21	110	−	86
5	c: 1-butylamine	5	2	110	53[a]	−
6	c: 1-butylamine	12	2.5	110	19[a]	68[a]
7	d: 2-butylamine	6.2	1.5	30	69[a]	−
8	e: *tert*-butylamine	5	4	110	65[a]	−
9	f: (*S*)-1-phenyl-ethylamine	1.8	2	40	30[a]	−
10	g: allylamine	6.2	20	75	−	68[b]
11	g: allylamine	6.2	1.75	95	77[a]	12[a]
12	h: *N*-buty-methylamine	12.5	2	30	17[a]	38[a]
13	i: benzylthiol	2.5	3	60	−	63[a,c]
14	k: dodecylthiol	1.9	2	70	−	23[a,c]

[a] isolated by column chromatography. [b] Isolated by crystallization. [c] Starting material recovered.

Scheme 6. **Unsymmetrical substitution of pyridine-*N*-oxide 17b**



Although diamine **2** was accessible via this sequence in multigram quantities, this route was considered to be not suitable for scale-up due to unpredictable safety risks in the synthetic sequence on larger scale. The new Kilolab synthesis avoids the potentially hazardous steps by devising a new route encompassing the regioselective bis-amination in positions 2 and 6 of 2,4,6-tribromopyridine-*N*-oxide **14** and subsequent reduction of the resulting *N*-oxides **15a,b** with iron under acidic conditions. Conversion of bis-benzylamine derivative **16** was easily accomplished under acidic conditions to also give access to bis-amine **2**. This new route allowed access to the desired 2,6-diamino-4-bromopyridine **2** in four or five steps from commercially available starting material with 28 or 33% overall yield, respectively. Additionally, this concept has allowed for the synthesis of further symmetrical monoamino pyridine *N*-oxides **15** and unsymmetrically substituted pyridine *N*-oxide derivatives **17** and **18** in good yields.

Experimental Section

4-Bromopyridine-2,6-dicarboxylic Acid Diethyl Ester (4). A mixture of 4.0 g (20 mmol) of chelidamic acid monohydrate **3** and 34.4 g (80 mmol) of PBr_5 in 60 mL of CCl_4 was heated to reflux for 12 h and afterwards cautiously treated with 20 mL of ethanol. After 30 min at 80 °C the mixture was cooled to room temperature, and the volatile components were distilled off under reduced pressure. The remaining residue was treated with 200 mL of ice−water mixture and stirred for 1 h. The white precipitate was filtered off, washed with water, and dried in high vacuum to yield

5.6 g (93%) of **4**. Anal. Calcd for $C_{11}H_{12}BrNO_4$: C, 43.73; H, 4.00; N, 4.64; Br, 26.45. Found: C, 43.90; H, 4.01; N, 4.65; Br, 26.54. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.46 (t, 6H, J = 2.9 Hz, CH_3), 4.51 (q, 4H, J = 2.9 Hz, OCH_2), 8.42 (s, 2H, H3,5). Mp 94 °C.

4-Bromopyridine-2,6-dicarboxylic Acid Dihydrazide (5). A solution of 4.8 g (15.7 mmol) of 4-bromopyridine-2,6-dicarboxylic acid diethyl ester **4** in 87 mL of ethanol was treated with 18.3 mL of a 24% solution of hydrazine in water and heated to 80 °C. The formed white suspension was filtered hot, and the collected precipitate was dried to yield 4.8 g (90%) of a white amorphous solid **5**. Anal. Calcd for $C_7H_8BrN_5O_2$: C, 30.68; H, 2.94; N, 25.55; Br, 29.15. Found: C, 31.11; H, 2.93; N, 25.00; Br, 28.92. ^{1}H NMR (DMSO-d_6, 250 MHz) δ 4.69 (s, br, 4H, NH_2), 8.25 (s, 2H, H3,5), 10.68 (s, br, 2H, NH). Mp > 240 °C.

4-Bromopyridine-2,6-diamine (2). A suspension of 1 g (3.65 mmol) of 4-bromopyridine-2,6-dicarboxylic acid dihydrazide **5** in 32 mL of water was treated with 1.6 mL of HCl (37%) at room temperature. The resulting mixture was cooled to 0 °C, and 554 mg of $NaNO_2$ in 2.4 mL of water was added slowly, maintaining the temperature below 2 °C. Upon completion of this addition, saturated $NaHCO_3$ solution was added to pH ~8, and the white precipitate was filtered off and washed with water. The residue was dissolved in $CHCl_3$ and dried with $MgSO_4$. The filtrate was concentrated below 10 °C to yield 970 mg (90%) of a white amorphous solid **6**. CAUTION: Azides tend to be potentially explosive.

A sample of 450 mg (1.5 mmol) of the white residue **6** was suspended in 6 mL of toluene/*tert*-butyl alcohol 5/1. After refluxing for 12 h the solvent was removed under reduced pressure, and 5 mL of toluene and 0.3 mL of trifluoroacetic acid were added and refluxed for 2 h. The solvents were removed, and the residue was purified by flash chromatography on silica eluting with DCM/methanol, 9/1. After removal of the solvents the title compound **2** was liberated through addition of 1 N NaOH to a suspension of the residue in diethyl ether. The organic phase was dried with Na_2SO_4, and the solvents were removed under reduced pressure, yielding 209 mg (74%) of the product **2** as white solid. Anal. Calcd for $C_5H_6BrN_3$: C, 31.94; H, 3.22; N, 22.35; Br, 42.50. Found: C, 32.02; H, 3.33; N, 21.77; Br, 41.84. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.29 (s, br, 4H, NH_2), 6.05 (s, 2H, H3,5). Mp 124.5 °C.

2,6-Dibromopyridine-1-oxide (12). To a solution of 4 kg (16.8 mol) of 2,6-dibromopyridine **11** in 20 L of trifluoroacetic acid was added 4.25 L of aqueous hydrogen peroxide (33%) (41 mol) in 1 h. The mixture was heated to 95−100 °C for 4 h. The mixture which contained 6% starting material was cooled to 25 °C and diluted with 5 L of water, whereupon the starting material formed a precipitate, which was filtered off. The product was extracted from the aqueous phase with 3 × 60 L of DCM. To remove all acid, the DCM phase was washed with 3 × 24 L of 0.5 M K_2CO_3 solution. DCM was evaporated under addition of hexane at atmospheric pressure. The suspension was cooled to 25 °C and filtered off, yielding 3.42 kg (80%) of product **12** as a white solid. Anal. Calcd for $C_5H_3Br_2NO$: C, 23.75; H, 1.20; N, 5.54; Br, 63.19. Found: C, 23.78; H, 1.33; N, 5.50; Br, 63.34. M^+ = 253. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.94 (t, 1H, J = 8 Hz, H4), 7.68 (d, 2H, J = 8 Hz, H3,5). Mp 186−187 °C.

2,6-Dibromo-4-nitropyridine-1-oxide (13). To a mixture of 10.9 L of concentrated sulphuric acid and 4.7 L of fuming nitric acid was added all at once 3.32 kg (13.09 mol) of 2,6-dibromopyridine-1-oxide **12**, and the mixture was stirred for 20 h at 60 °C. After completion of the reaction, the mixture was neutralised with ammonium hydroxide and ice. The precipitate was filtered and dried to yield 3.65 kg of product **13** (93%) as a white solid. Anal. Calcd for $C_5H_2Br_2N_2O_3$: C, 20.16; H, 0.68; N, 9.40; Br, 53.65. Found: C, 20.13; H, 0.76; N, 9.42; Br, 53.66. M^+ = 332. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.50 (s, 2H, H3,5).

2,4,6-Tribromopyridine-1-oxide Hydrobromide (14). A suspension of 140.2 g (0.47 mol) of 2,6-dibromo-4-nitropyridine-1-oxide **13** in 2260 mL of acetic acid was warmed to 60 °C, and 35.4 mL (0.476 mol) of acetyl bromide was added. The reaction mixture was stirred at 80 °C for 5 h. After completion of the reaction, the mixture was cooled to 15 °C and the product isolated by filtration. The precipitate was washed with 500 mL of diethyl ether to remove residual acetic acid and dried to yield 129.6 g (67%) of the hydrobromide **14** as a white solid. Anal. Calcd for $C_5H_2Br_3$-NO HBr: C, 14.55; H, 0.73; N, 3.39. Found: C, 14.47; H, 0.94; N, 3.25. M^+ = 298. ^{1}H NMR (DMSO, 400 MHz) δ 8.31 (s, 2H, H3,5).

General Procedure for the Reaction of 2,4,6-Tribromopyridine-1-oxide Hydrobromide (14) with Nucleophiles b−k. A mixture of starting material **14** and the nucleophile in toluene was heated for the indicated time (for conditions, see Table 1). (Initially, 2 equiv of K_2CO_3 was added to speed up to the reaction; later it turned out that additional base did not affect the reaction.) After completion of the reaction, the mixture was cooled to ambient temperature, diluted with water, and extracted with ethyl acetate. The residue was purified by crystallisation or column chromatography.

4,6-Dibromo-1-oxypyridin-2-ylamine (17a). A suspension of 2 g (4.84 mmol) of **14** in 14 mL of 33% aqueous ammonium hydroxide solution was heated for 3 h at 110 °C in a sealed tube. After extraction, the product was purified by column chromatography on silica, eluting with DCM/ethanol, 3/1, to yield 170 mg (13%) of the desired product as a white powder. M^+ = 268. ^{1}H NMR (DMSO, 400 MHz) 6.95 (d, 1H, J = 2.8 Hz, H3), 7.28 (d, 1H, J = 2.8 Hz, H5), δ 7.29 (s, 2H, NH_2).

4-Bromo-1-oxypyridine-2,6-diamine (15a). A suspension of 48.8 g (118 mmol) of **14** in 144 mL of 33% aqueous ammonium hydroxide solution was heated under magnetic stirring in a sealed tube at 140 °C for 5 h. The reaction mixture was cooled to 0 °C, and the precipitate was filtered off, washed with 100 mL of ice−water, and dried to yield 18.4 g (76%) of the desired product as dark brown needles. Anal. Calcd for $C_5H_6BrN_3O$: C, 29.44; H, 2.96; N, 19.05. Found: C, 29.34; H, 2.64; N, 20.14. M^+ = 204. ^{1}H NMR (DMSO, 400 MHz) δ 6.12 (s, 2H, H3,5), 6.79 (s, 4H, NH_2). Mp 105−107 °C.

Benzyl-(4,6-dibromo-1-oxypyridin-2-yl)amine (17b). A mixture of 60 g (145.38 mmol) of **14** suspended in 800 mL of toluene was reacted with 97 g (905.18 mmol) of benzylamine at 70 °C for 2 h. After extraction the product was purified by column chromatography on silica eluting with DCM/ethanol, 98/2, to yield 6.83 g (12.1%) of **15b** and 38.23 g (73.4%) of **17b** as white powder. Anal. Calcd for $C_{12}H_{10}Br_2N_2O$: C, 40.26; H, 2.82; N, 7.82; Br, 44.63. Found: C, 40.22; H, 2.95; N, 7.88, Br, 44.34. $M^+ = 358$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.29 (d, 2H, $J = 6.4$ Hz, CH_2Ph), 6.61 (d, 1H, $J = 2.4$ Hz, H3), 7.09 (d, 1H, $J = 2.4$ Hz, H5), 7.30−7.39 (m, 5H, Ph), 7.52 (m, br, 1H NH). Mp 154−155 °C.

***N,N′*-Dibenzyl-4-bromo-1-oxypyridine-2,6-diamine (15b).** A mixture of 50 g (121.1 mmol) of **14** suspended in 700 mL of toluene was reacted with 129 g of benzylamine (1.21 mol) and 52.2 g of K_2CO_3 for 21 h at 110 °C. After extraction the product was purified by crystallisation from DCM/TBME to yield 40.3 g (86.5%) of **15b** as beige crystals. $M^+ = 384$. ^{1}H NMR (DMSO, 400 MHz) δ 4,46 (d, 4H, $J = 6.4$ Hz, 2 × CH_2Ph), 6.08 (s, 2H, H3,5), 7.22−7.27 (m, 2H, Ph), 7.32−7.33 (m, 8H, Ph) 7.38 (t, br, 2H, $J = 6.4$ Hz, NH). Mp 176−178 °C.

Butyl-(4,6-dibromo-1-oxypyridin-2-yl)amine (17c). A mixture of 5 g (12.11 mmol) of **14** suspended in 80 mL of toluene was reacted with 4.31 g (58.8 mmol) of *N*-butylamine at 110 °C for 2 h. After extraction the product was purified by column chromatography on silica eluting with hexane/ethyl acetate, 1/2, to yield 2.1 g (53%) of **15c** as a yellow residue. $M^+ = 324$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (t, 3H, $J = 7.2$ Hz, CH_3), 1.45 (sex, 2H, $J = 7,2$ Hz, $C\underline{H}_2CH_3$), 1.68 (qui, 2H, $J = 7.2$ Hz, $NCH_2C\underline{H}_2$), 3.45 (q, 2H, $J = 7.2$ Hz, NCH_2), 6.64 (d, 1H, $J = 2.4$ Hz, H3), 7.03−7.06 (m, 2H, NH,H5).

4-Bromo-*N,N′*-dibutyl-1-oxypyridine-2,6-diamine (15c). A mixture of 5 g (12.11 mmol) of **14** suspended in 90 mL of toluene was reacted with 4.11 g (147.3 mmol) of *N*-butylamine for 2.5 h at 110 °C. After extraction the product was purified by column chromatography on silica eluting with hexane/ethyl acetate, 1/2, to yield 0.75 g (19.1%) of **17c** and 2.62 g (68.3%) of **15c** as a light yellow residue. $M^+ = 316$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, 6H, $J = 7.2$ Hz, 2 × CH_3), 1.44 (sex, 4H, $J = 7.2$ Hz, 2 × $C\underline{H}_2CH_3$), 1.66 (qui, 4H, $J = 7.2$ Hz, 2 × $NCH_2C\underline{H}_2$), 3.20 (q, 4H, $J = 7.2$ Hz, 2 × NCH_2), 5.99 (s, 2H, H3,5), 6.65−6.75 (m, 2H, NH).

***sec*-Butyl-(4,6-dibromo-1-oxypyridin-2-yl)amine (17d).** A mixture of 5 g (12.11 mmol) of **14** suspended in 90 mL of toluene was reacted with 5.55 g (75.53 mmol) of *sec*-butylamine for 1.5 h at 30 °C. After extraction the product was purified by column chromatography on silica eluting with hexane/ethyl acetate, 1/3, to yield 2.70 g (68.7%) of **17d** as a light yellow solid. $M^+ = 324$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (t, 3H, $J = 7.2$ Hz, $CH_2C\underline{H}_3$), 1.44 (t, 3H, $J = 6.6$ Hz, $CHC\underline{H}_3$), 1.59−1.71 (m, 2H, $C\underline{H}_2CH_3$), 3.38−3.45 (m, 1H, NCH), 6.63 (d, 1H, $J = 2.4$ Hz, H3), 6.99 (d, br, 1H, $J = 8$ Hz, NH), 7.03 (d, 1H, $J = 2.4$ Hz, H5).

***tert*-Butyl-(4,6-dibromo-1-oxypyridin-2-yl)amine (17e).** A mixture of 5 g (12.11 mmol) of **14** suspended in 90 mL of toluene was reacted with 4.46 g (60.97 mmol) of *tert*-butylamine at 110 °C for 4 h. After extraction, the product was purified by column chromatography on silica eluting with hexane/ethyl acetate, 1/3, to yield 2.54 g (64.7%) of **17e** as a yellow solid. $M^+ = 324$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H, 3 × $C\underline{H}_3$), 6.85 (d, 1H, $J = 2.4$ Hz, H3), 7.03 (d, 1H, $J = 2.4$ Hz, H5), 7,4 (s, br, 1H, NH).

***S*-(4,6-Dibromo-1-oxypyridin-2-yl)-(1-phenylethyl)-amine (17f).** A mixture of 2 g (4.85 mmol) of **14** suspended in 30 mL of toluene was reacted with 1.096 g (9.04 mmol) of (*S*)(−)-α-methylbenzylamine at 40 °C for 2 h. After extraction, the product was purified by column chromatography on silica eluting with hexane/ethyl acetate, 1/3, to yield 0.54 g (29.9%) of **17f** as a colourless solid. $M^+ = 372$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65 (d, 3H, $J = 6.8$ Hz, $C\underline{H}_3$), 4.53 (qui, 1H, $J = 6.8$ Hz, NCH), 6.47 (d, 1H, $J = 2.4$ Hz, H3), 7.04 (d, 1H, $J = 2.4$ Hz, H5), 7.25−7.40 (m, 5H, Ph), 4.56 (d, 1H, $J = 6.8$ Hz, NH). $\alpha^{20}_D = +96.4$ ($c = 1\%$, $CHCl_3$).

***N,N′*-Diallyl-4-bromo-1-oxypyridine-2,6-diamine (15g).** A mixture of 4.9 g (11.8 mmol) of **14** suspended in 75 mL of toluene was reacted with 4.48 g (75 mmol) of allylamine and 5.2 g of K_2CO_3 at 75 °C for 20 h. After extraction the product was purified by crystallisation from DCM/isopropyl ether to yield 2.27 g (67.7%) of **15g** as reddish crystals. Anal. Calcd for $C_{11}H_{14}BrN_3O$: C, 46.50; H, 4.97; N, 14.79. Found: C, 46.44; H, 4.90; N, 14.71.$M^+ = 284$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85−3.95 (m, 4H, 2 × NCH_2), 5.20−5.33 (m, 4H, 2 × $CHC\underline{H}_2$olef), 5.84−5.94(m, 2H, 2 × $C\underline{H}CH_2$olef), 6.03 (s, 2H, H3,5), 6.9 (br, 2H, 2 × NH). Mp 93−94 °C.

Allyl-(4,6-dibromo-1-oxypyridin-2-yl)amine (17g). A mixture of 10 g (24.23 mmol) of **14** suspended in 150 mL of toluene was reacted with 8.62 g (150.96 mmol) of allylamine at 95 °C for 1.75 h. After extraction, the product was purified by column chromatography on silica eluting with DCM/ethanol, 20/1, to yield 0.83 g (12%) of **15g** and 5.49 g (77.5%) of **17g** as a yellow solid. $M^+ = 308$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.91−3.96 (m, 2H, NCH_2), 5.25−5.35-(m, 2H, $CHC\underline{H}_2$), 5.82−5.93 (m, 1H, $C\underline{H}CH_2$), 6.64 (d, 1H, $J = 2.8$ Hz, H3), 7.09 (d, 1H, $J = 2.8$ Hz, H5), 7.2 (br, 1H, NH). Mp 109 °C.

Butyl-(4,6-dibromo-1-oxypyridin-2-yl)methylamine (17h) and 4-Bromo-*N,N′*-dibutyl-*N,N′*-dimethyl-1-oxypyridine-2,6-diamine (15h). A mixture of 5 g (12.11 mmol) of **14** suspended in 90 mL of toluene was reacted with 8.62 g (150.96 mmol) of *N*-methylbutylamine for 2 h at 30 °C. After extraction, the product was purified by column chromatography on silica eluting with ethyl acetate/hexane, 3/1, to yield 0.680 g (16.9%) of **17h** as a colorless oil. $M^+ = 338$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, 3H, $J = 7.2$ Hz $CH_2C\underline{H}_3$), 1.32 (sex, 2H, $J = 7,2$ Hz, $C\underline{H}_2CH_3$), 1.55−1.67 (m, 2H, $NCH_2C\underline{H}_2$), 2.97 (s, 3H, NCH_3), 3.56 (t, 2H, $J = 7.6$ Hz, $NC\underline{H}_2$), 6.86 (d, 1H, $J = 2.4$ Hz, H3), 7.40 (d, 1H, $J = 2.4$ Hz, H5). **15h**: 1.96 g (38.3%) of colorless oil $M^+ = 344$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, 6H, $J = 7.2$ Hz, 2 ×

$CH_2C\underline{H}_3$), 1.28 (sex, 4H, J = 7.2 Hz, 2 × $C\underline{H}_2CH_3$), 1.49−1.57 (m, 4H, 2 × $NCH_2C\underline{H}_2$), 2.93 (s, 6H, 2 × NCH_3), 3.47 (t, 4H, J = 7,6 Hz, 2 × $NC\underline{H}_2$), 6.53 (s, 2H, H3,5).

2,6-Bis-benzylsulfanyl-4-bromopyridine-1-oxide (15i). A mixture of 5 g (12.11 mmol) of **14** suspended in 100 mL of toluene was reacted with 3.74 g (30.14 mmol) of benzyl mercaptane and 3.38 g of potassium *tert*-butoxide (30.14 mmol) for 3 h at 60 °C. After extraction, the product was purified by column chromatography on silica eluting with DCM/ethyl acetate/hexane, 10/1/1, to yield 3.21 g (63.3%) of **15i** as a colourless solid. M^+ = 418. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.13 (s, 4H, 2 × $C\underline{H}_2$Ph), 7.00 (s, 2H, H3,5), 7.25−7.45 (m, 10H, 2 × Ph). mp. 205−206 °C.

4-Bromo-2,6-bis-dodecylsulfanylpyridine-1-oxide (15k). A mixture of 5 g (12.11 mmol) of **14** suspended in 100 mL of toluene was reacted with 4.58 g (22.6 mmol) of 1-dodecanethiol and 2.54 g of potassium *tert*-butoxide (22.6 mmol) for 2 h at 70 °C. After extraction the product was purified by column chromatography on silica eluting with DCM/ethanol, 98/2, to yield 1.6 g (22.9%) of **15k** as white crystals. M^+ = 574. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 6H, J = 6.8 Hz, 2 × CH_3), 1.26−1.32 (m, 32H, 16 × CH_2), 1.45−1.53 (m, 4H, 2 × CH_2), 1.72−1.80 (m, 4H, 2 × CH_2), 2.85 (t, 4H, J = 7.2 Hz, 2 × SCH_2), 6.93 (s, 2H, H3,5). Mp 86−87 °C.

4-Bromopyridine-2,6-diamine (2). A mixture of 41.6 g (203.9 mmol) of **15a** and 13.65 g of iron (244.4 mmol) in 200 mL of acetic acid/water 1:1 was stirred at 100 °C for 2 h. The mixture was cooled to 25 °C, diluted with 700 mL of ethyl acetate, and neutralised with 28% NaOH. To remove solid parts, the whole mixture was filtered over 100 g of silica. The layers were separated, and the organic layer was washed with 800 mL of brine. The aqueous layers were extracted consecutively with 700 mL of ethyl acetate. The organic solvent was evaporated to yield 30.55 g of black solid. This was dissolved in 120 mL of ethyl acetate and filtered through 150 g of silica eluting with ethyl acetate. The solvent was evaporated, and the residue was crystallised from ethyl acetate/DCM to yield 22.8 g (59.4%) as beige crystals, which were identical to the title compound **2**.

***N,N′*-Dibenzyl-4-bromopyridine-2,6-diamine (16).** A mixture of 40 g (104 mmol) of **15b** and 7.05 g of iron (126 mmol) in 400 mL of acetic acid/water, 1:1, was stirred at 90 °C for 4 h. The mixture was cooled to 25 °C, diluted with 1000 mL of ethyl acetate, and neutralised with 28% NaOH. To remove solid parts, the whole mixture was filtered over 100 g of silica. The layers were separated, and the organic layer was washed with 700 mL of water. The organic solvent was evaporated to yield 39 g of black solid, which was dissolved in 40 mL of DCM and filtered on 150 g of silica with DCM. The solvent was evaporated to yield 36 g (93.9%) of **16** as a slightly green solid. Anal. Calcd for $C_{19}H_{18}BrN_3$: C, 61.97; H, 4.93; N, 11.41; Br, 21.70. Found: C, 61.90; H, 4.93; N, 11.36; Br, 21.67. M^+ = 368. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.42 (d, 4H, J = 6.0 Hz, 2 × CH_2Ph), 4.66 (br, 2H, NH), 6.91 (s, 2H, H3,5), 7.12−7.35 (m, 10H, 2 × Ph). Mp 85 °C.

4-Bromopyridine-2,6-diamine (2). To 100 mL of sulphuric acid was added 20 g (54.3 mmol) of **15b** within 2 min. The mixture was stirred for 1.5 h at 40 °C. The mixture was added to 500 g of ice, neutralised with 300 mL of ammonium hydroxide (25%), and extracted twice with 500 mL of ethyl acetate. The organic layers were washed with 600 mL of water, dried, and concentrated to yield 8.2 g of beige solid. This solid was filtered with ethyl acetate over 40 g of silica, and the solvent was evaporated. The residue was crystallised from 120 mL of DCM to yield 7 g (68.5%) of beige needles, which were identical with the title compound **2**.

***N*-Benzyl-4-bromo-*N′*-butyl-1-oxypyridine-2,6-diamine (18).** A mixture of 4 g (11.17 mmol) of monobenzyl derivative **17b** suspended in 90 mL of toluene was reacted with 1.81 g (24.6 mmol) of butylamine for 4 h at 111 °C. After extraction, the product was purified by column chromatography on silica eluting with ethyl acetate/hexane, 3/1, to yield 1.9 g (48%) of **18** as white crystals Anal. Calcd for $C_{16}H_{20}BrN_3O$: C, 54.87; H, 5.76; N, 12.00; Br, 22.81. Found: C, 54.78; H, 5.69; N, 11.97, Br, 23.02. M^+ = 350. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, 3H, J = 7.2 Hz, CH_3), 1.45 (sex, 2H, J = 7.2 Hz, $C\underline{H}_2CH_3$), 1.68 (qui, 2H, J = 7.2 Hz, $NCH_2C\underline{H}_2$), 3.21 (q, 2H, J = 6.9 Hz, NCH_2), 5.98 (d, 1H, J = 2.0 Hz, H5), 6.04 (d, 1H, J = 2.0 Hz, H3), 6.7 (br, 1H, NH), 7.1 (br, 1H, NH), 7.7.20−7.38 (m, 5H, Ph). Mp 96 °C.

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