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## SYNTHETIC STUDIES OF SUBSTITUTED PYRIDINE ALDEHYDES AS INTERMEDIATES FOR THE SYNTHESIS OF TODDAQUINOLINE, ITS DERIVATIVES AND OTHER NATURAL PRODUCTS

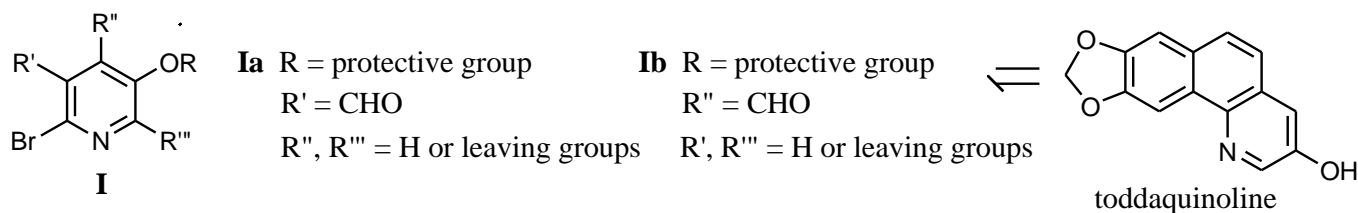
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**Abstract** – The synthesis of substituted 2-bromopyridine aldehydes as intermediates in our planned approach to toddaquinoline, its derivatives and other natural products is reported. The DMF-formylation method of pyridine ring, the Vilsmeier-Haack procedure and the bromination of pyridine ring respectively, were studied in order to synthesize the above mentioned compounds. The successful methods (DMF-formylation and bromination of pyridine ring) provided the 2-bromo-4-formyl-5-tosyloxy pyridine **Ib** and 5-benzyloxy-2,4,6-tribromonicotinaldehyde **Ia** under relatively mild conditions and in good yields.

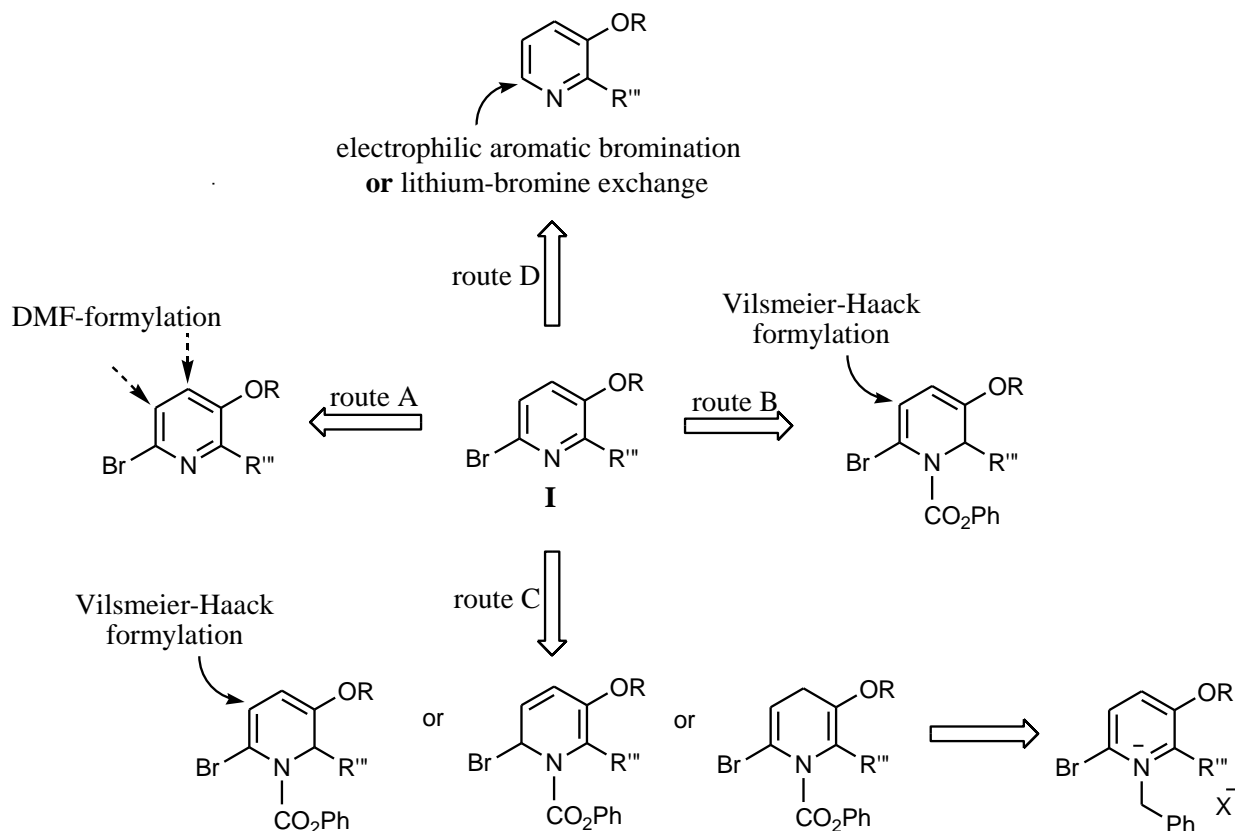
### INTRODUCTION

Toddaquinoline, a benzo[*h*]quinoline alkaloid featuring a unique tetracyclic skeleton, was isolated in 1993 from the root bark of *Toddalia asiatica*, a constituent of many Asian folk medicines.<sup>1a,b</sup> In connection with our efforts to develop new and useful methods for the preparation of the *Toddalia asiatica* alkaloids<sup>2</sup> and other natural products, our need for syntheses led us to prepare functionalized pyridine aldehydes type **I**, particularly molecules that bear bromine and hydroxyl functional groups.



## RESULTS AND DISCUSSION

Taking into account the chemical literature concerning the pyridines being substituted with formyl or bromine group respectively, we focused on the possibilities of obtaining the substituted 2-bromopyridine aldehydes **I** and our synthetic approach is based on the four routes as shown in the retrosynthetic analysis (Scheme 1).

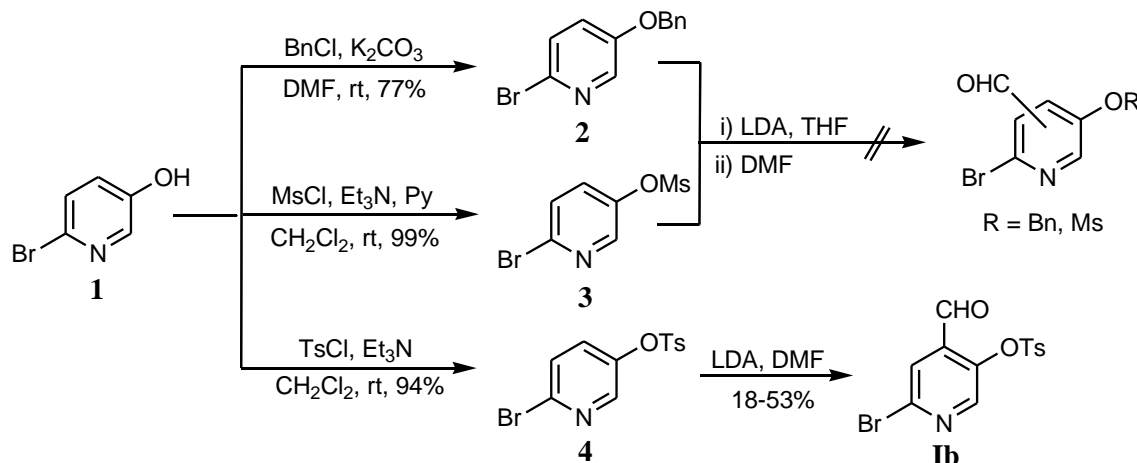


**Scheme 1.** Retrosynthesis of compounds **I**

### Pyridine ring formylation by DMF (route A)

Lithiation of aromatic and heteroaromatic compounds has been widely used to introduce various functional groups. This reaction is a very efficient functionalization method since electrophilic substitutions are often difficult on  $\pi$ -deficient heterocycles. 2-Bromopyridine aldehyde and its derivatives are valuable intermediates in heterocyclic chemistry. *ortho*-Bromopyridine aldehydes have been prepared by *ortho*-metalation of bromopyridines with lithium diisopropylamide LDA followed by electrophilic substitution with DMF.<sup>3a-c</sup> Based upon the fact that the *ortho*-metalation procedure studied previously in our laboratory<sup>2</sup> is a useful route for the synthesis of various 2-bromopyridine aldehydes, our first strategy involved the pyridine ring formylation by DMF (route A). Subsequently the protection of hydroxyl group as benzyl,<sup>4</sup> mesyl and tosyl,<sup>5</sup> we started to investigate the reaction of 2-bromo-5-hydroxypyridine with LDA and DMF under various conditions.

Since in our previous studies the formylation of pyridine ring worked very well when 3 eq LDA/4 eq DMF/THF/-78 °C were used,<sup>2</sup> in this case the first experiments using as starting materials 2-bromo-5-benzyloxy pyridine **2** and 2-bromo-5-mesyloxy pyridine **3** respectively, did not give the expected formylated products except the recovery of the starting materials in very high yields. Different experimental conditions still did not improve the result. Further we used 2-bromo-5-tosyloxy pyridine **4** as starting material for the pyridine ring formylation by DMF (Scheme 2).



**Scheme 2.** Formylation by DMF of compound **1**

The formylation of 2-bromo-5-tosyloxy pyridine **4** proved to be also troublesome in the above mentioned experimental conditions giving only the starting material in a very high yield (table 1, run 1). A higher reaction temperature (-80 °C → -40 °C) did not give a better result (run 2). By increasing the amount of deprotonation agent to 10 eq of LDA, the reaction proceeded in one case (run 3). When the reaction conditions of run 3 were applied again, the result could not be reproduced in the next experiments. Only when a different solvent (THF → ether) and higher amounts of deprotonation agent/formylation agent (10 eq LDA/4-8 eq DMF) were used, the formyl compound was obtained in a moderate to good yield (run 4-6).

**Table 1.** The results of the formylation of compound **4**

Run	LDA (eq/time)	DMF (eq/time)	solvent	temp (°C)	yield (%)	
					<b>4</b>	<b>Ib</b>
1.	3/1h	4/1h	THF	-78	96	-
2.	3/2h	4/1.5h	THF	-40	97	-
3.	10/1.5h	4/1h	THF	-80	-	43
4.	10/1.5-2h	4/1h	Et <sub>2</sub> O	-75	43	18
5.	10/2h	6/1h	Et <sub>2</sub> O	-78	-	43
6.	10/1.5-2h	8/1h	Et <sub>2</sub> O	-80	-	53

The position of formyl group of the compound **Ib** was assigned by one- ( $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ ) and two-dimensional experiments (HMBC), which showed the correlation of formyl hydrogen with  $\text{C}_3$ ,  $\text{C}_4$  and  $\text{C}_5$  of the pyridine ring meaning that deprotonation/formylation proceeded on the *ortho*-position of the functional group containing oxygen.<sup>6a,b</sup>

### Pyridine ring formylation by Vilsmeier-Haack procedure (route B-C)

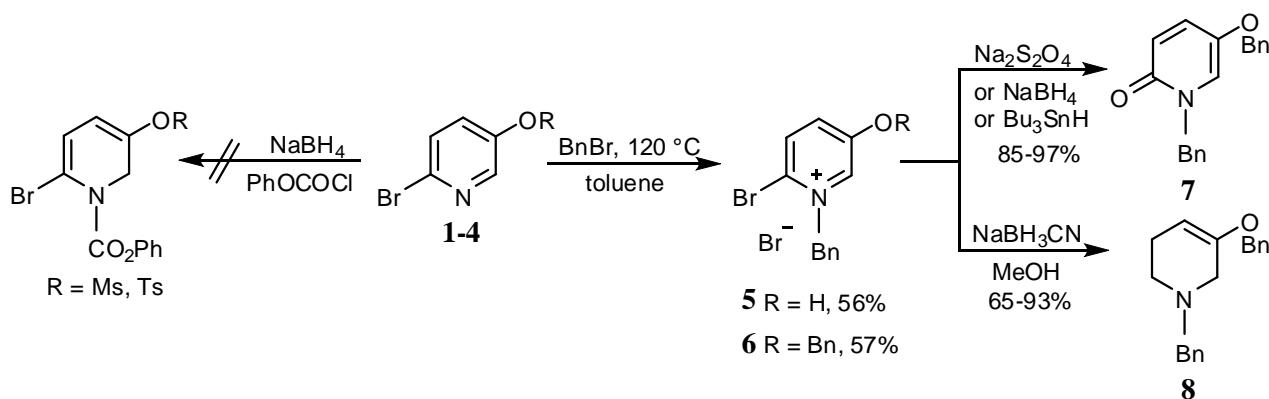
The Friedel-Crafts acylation and Vilsmeier formylation, which are important methods for the preparation of aryl ketones and aldehydes, fail in the pyridine series, making many 3-pyridine ketones and 3-pyridine carboxaldehydes difficult to prepare.<sup>7a</sup> In the last years, there have been developed synthesis of substituted pyridines via *N*-acyldihydropyridine or *N*-alkylpyridinium salts intermediates.<sup>7-c</sup> The 1,2- and 1,4-dihydropyridine have proven to be valuable intermediates for the preparation of interesting heterocyclic compounds. Meanwhile, 1,2-dihydropyridines that do not contain electron-withdrawing substituents on the ring are unstable, *N*-acyl-1,2-dihydropyridine are stabilized by the acyl group.<sup>8a,b</sup> The  $\beta$ -position of a 1-acyldihydropyridine is electron rich and susceptible to electrophilic attack. Shono<sup>9</sup> described one example of  $\beta$ -formylation of 1-acyl-1,4-dihydropyridine and Comins reported the  $\beta$ -formylation of some substituted 1-(phenoxy-carbonyl)-1,2-dihydropyridines via Vilsmeier-Haack reaction. The regiospecific  $\beta$ -formylation of 1-acyldihydropyridines has considerable potential for the synthesis of substituted 3-pyridine carboxaldehydes.<sup>7a,b</sup>

The preparation of compound **Ia** requires a method for the synthesis of *N*-acyl-6-bromo-3-hydroxy-1,2-dihydropyridine (route B). Comins synthesized the 3-substituted 1-(phenoxy-carbonyl)-1,2-dihydropyridines using Fowler's method by the reaction of several 3-substituted pyridines with phenyl chloroformate and sodium borohydride in methanol at  $-78\text{ }^\circ\text{C}$ .<sup>7a</sup> Although Fowler and Comins have developed excellent procedures for the preparation of *N*-carboxyalkyl and *N*-carboxyphenyl 1,2-dihydropyridines, when these procedures were applied to 2-bromo-5-mesyloxy-pyridine **3** and 2-bromo-5-tosyloxy-pyridine **4** respectively, no reaction was found to occur and we recovered the unreacted starting material in every cases. The change of solvent (methanol $\rightarrow$ ether), higher amounts of reductive agent or acylation agent (concentration of sodium borohydride and phenyl chloroformate ranging from 1.3 eq and 1 eq, respectively to 2.5-3 eq) or varying the reaction temperature did not provide the desired *N*-acyl-6-bromo-3-hydroxy-1,2-dihydropyridine, the key intermediate for the formylation step (Scheme 3).

Further we studied the use of pyridinium salts as activated electrophilic substrates for reduction. The intermediate generated by the reduction of such salts can be reacted successfully with a range of different electrophiles (e.g. carbonyl compounds to give *N*-acyldihydropyridine).<sup>10</sup> There are very few examples of 2-bromopyridine being *N*-alkylated using a suitable alkyl chain, the reluctance of 2-halopyridines to undergo alkylation with normal type of alkyl halides and tosylates being known.<sup>7d,e</sup> Thus, we decided to try the benzyl halides which have been used to synthesize *N*-benzylpyridinium salts in other examples<sup>11a,b</sup>

and the *N*-alkylation was achieved in good yield when benzyl bromide was used (route C, Scheme 3). Having the 2-bromo-5-hydroxy-*N*-benzylpyridinium bromide **5** and 2-bromo-5-benzyloxy-*N*-benzylpyridinium bromide **6** in hands we focused on the reduction of the pyridinium salts. Earlier reports on the reduction of some pyridinium salts indicated that the selective formation of single dihydro isomer is difficult and dependent on temperature, pH and the nature of the reducing agent.<sup>12a,b</sup> Thus, the reduction of 2-bromo-5-hydroxy-*N*-benzylpyridinium bromide **5** by sodium borohydride, lithium aluminium hydride and sodium cyanoborohydride proved unsuccessful, in as much as many organic products very difficult to separate could be extracted from the reaction mixture.

With this background information, we carried out detailed studies on the reduction of 2-bromo-5-benzyloxy-*N*-benzylpyridinium bromide **6** by sodium dithionite in alkaline medium, sodium borohydride and tributyltin hydride. Working under various conditions, attempts to obtain 1,2- or 1,4-dihydropyridines were disappointing, the only compound obtained being the hydrolysis product 5-benzyloxy-*N*-benzylpyridine-2-one **7**.



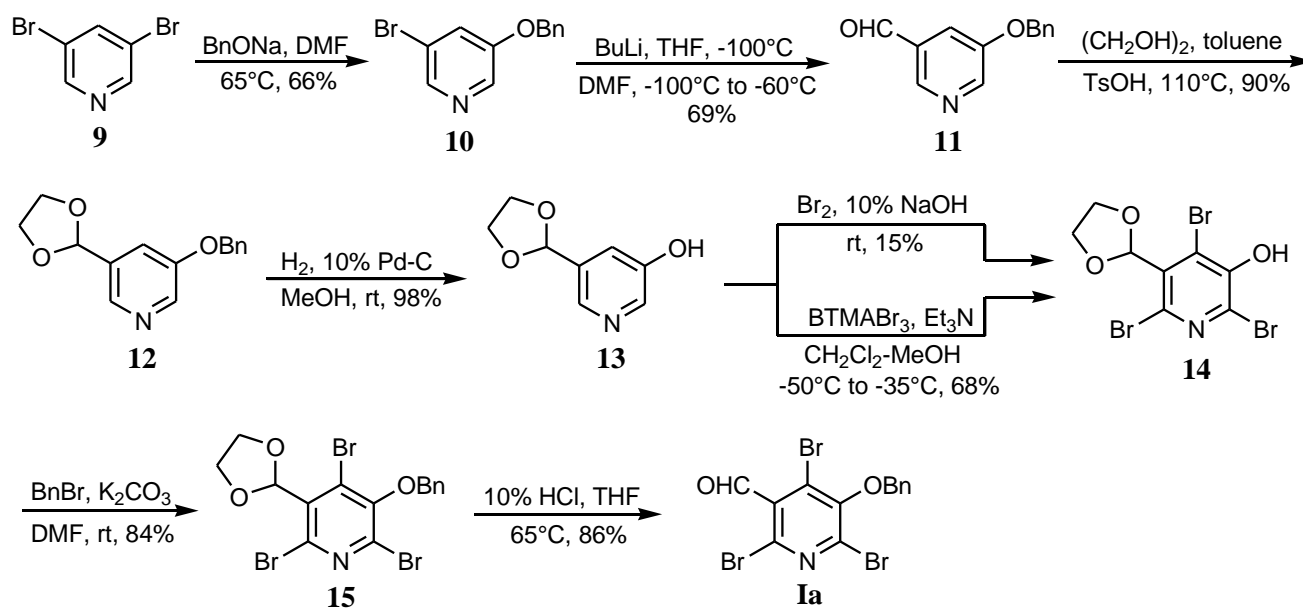
**Scheme 3.** *N*-Acylation/reduction and *N*-alkylation/reduction studies on compounds **1-4**

Selective sodium cyanoborohydride reduction in the nitrogen heterocyclic area and the conversion of certain pyridinium salts to the corresponding 1,2,5,6-tetrahydropyridines have been studied.<sup>13</sup> The conversion of 1,2,5,6-tetrahydropyridines to dihydropyridines by bromination/double dehydrobromination with ethyl aluminium dichloride in HMPA under mild conditions is also known.<sup>11b</sup> Despite our efforts, the reduction of **6** by sodium cyanoborohydride in methanol at reflux or at room temperature gave the corresponding debrominated 1,2,5,6-tetrahydropyridine **8**, not useful for bromination/double dehydrobromination step (Scheme 3).

#### Pyridine ring bromination (route D)

Our last approach for the preparation of compound **Ia** employed a bromination of the pyridine ring carrying the formyl group (route D, Scheme 4). The intermediate 5-benzyloxynicotinaldehyde **11**, prepared from 3,5-dibromopyridine **9** by a method previously described,<sup>14a,b</sup> after acetalization with ethylene glycol in toluene<sup>15</sup> yielded the corresponding 5-benzyloxynicotinaldehyde acetal **12**. Since our

experiments concerning the bromination of acetal **12** failed via electrophilic aromatic substitution ( $\text{Br}_2/\text{K}_2\text{CO}_3$ ,  $\text{Br}_2/\text{AcOH}$ , benzyltrimethylammonium tribromide  $\text{BTMABr}_3$ )<sup>16a-d</sup> and also via lithium-bromine exchange procedure ( $\text{LDA}/\text{NBS}$ ,  $n\text{-BuLi}/\text{NBS}$ ,  $n\text{-BuLi}/\text{DBTCE}$  dibromo tetrachloroethane,  $n\text{-BuLi}/\text{LiDMAE}/\text{NBS}$ ,  $n\text{-BuLi}/\text{LiDMAE}/\text{DBTCE}$ )<sup>17a,b</sup> catalytic  $\text{Pd}/\text{C}$  hydrogenolysis of compound **12** in methanol<sup>18</sup> gave debenzylated product **13** in a very good yield.



**Scheme 4.** Synthesis of 5-benzyloxy-2,4,6-tribromonicotinaldehyde **Ia**

**Table 2.** The results of the bromination of compound **13**

Run	$\text{Br}_2$ (eq)	$\text{BTMABr}_3$ (eq)	base (eq)	temp ( $^{\circ}\text{C}$ )	time (h)	yield (%)	
						<b>13</b>	<b>14</b>
1.	2	-	$\text{Na}_2\text{CO}_3$	rt	17	10	-
2.	1	-	$\text{NaOH}$	rt	1	-	15
3.	1	-	$\text{NaOH}$	0	2	-	16
4.	-	1.1	-	rt	23	many spots	
5.	-	1.01	-	0	1.5	-	6
6.	-	1.01	-	-45	3.5	-	22
7.	-	1.01	-	-78	1.5	-	10
8.	-	3	-	-40	3	-	37
9.	-	4	-	-35	40 min	-	48
10.	-	4	$\text{Et}_3\text{N}$ (6)	-50 to -35	3	-	68

Out of the bromination reagents tried the best was benzyltrimethylammonium tribromide  $\text{BTMABr}_3$  which reacted with hydroxypyridine **13** in dichloromethane-methanol mixture. Various reaction conditions were experimented and good yields of the bromo compound **14** were obtained when a base ( $\text{Et}_3\text{N}$ ) was employed in order to neutralize a generating hydrogen bromide. Reaction of equimolar

amounts of 3-hydroxypyridine **13** and bromine in the presence of a 10% aqueous solution of sodium hydroxide<sup>19a,b</sup> gave the brominated hydroxypyridine **14** only in low yield (15%). The results are summarized in the table 2.

In the next steps, the hydroxyl function was protected using the benzyl group<sup>4</sup> which proved to be a good leaving group for deprotection method and the acetal group of **15** was removed by 10% HCl in THF<sup>20</sup> to afford the 5-benzyloxy-2,4,6-tribromonicotinaldehyde **Ia**, a good intermediate for the synthesis of totdaquinoline and its derivatives.

In conclusion, we have developed highly practical and efficient syntheses of substituted 2-bromopyridine aldehydes **Ia** and **Ib** without using very expensive or dangerous reagents.

Due to reluctance of 2-bromopyridine for the introduction of substituents on its  $\pi$ -deficient aromatic ring, different synthetic pathways were studied: DMF-formylation method of pyridine ring, Vilsmeier-Haack formylation of *N*-acyl-1,2-dihydropyridine (starting from *N*-acyldihydropyridine or *N*-alkylpyridinium salts) and bromination of pyridine ring. The successful methods provided the 2-bromo-4-formyl-5-tosyloxy pyridine **Ib** from 2-bromo-5-hydroxypyridine in 2 steps by DMF formylation method and 5-benzyloxy-2,4,6-tribromonicotinaldehyde **Ia** from 3,5-dibromopyridine in 7 steps by means of benzyltrimethylammonium tribromide under relatively mild conditions and in good yields. To the best of our knowledge, this is the first attempt of hydroxypyridines bromination using BTMABr<sub>3</sub> as bromination reagent. The 2-bromopyridine aldehydes **Ia** and **Ib** are very good intermediates in the synthesis of totdaquinoline, its derivatives and other natural products.

## EXPERIMENTAL

**General:** Melting points were measured on a micro-melting point hot-stage apparatus (Yanagimoto) and are uncorrected. The IR spectra were recorded using a JASCO FTIR-350 spectrophotometer. The <sup>1</sup>H-NMR spectra in deuteriochloroform were recorded by a Mercury-300, VXR-500 or Varian Unity INOVA AS-600 spectrometer. The NMR spectral data are reported in parts per million downfield from the internal standard (tetramethylsilane,  $\delta$  0.0). The FAB-MS were obtained using a VG AutoSpec spectrometer with *m*-nitrobenzyl alcohol as the matrix. The elemental analysis was performed using a Yanaco MT-5 analyzer. Column chromatography was carried out with Merck silica gel (230-400 mesh). The TLC analysis was performed on Kieselgel 60 F<sub>254</sub> (Merck) plates. All the experiments were carried out in an argon atmosphere, unless otherwise noted.

**Substrates:** 2-bromo-5-benzyloxy pyridine **2**,<sup>4</sup> 2-bromo-5-tosyloxy pyridine **4**, 2-bromo-4-formyl-5-tosyloxy pyridine **Ib**,<sup>6b</sup> 3-bromo-5-benzyloxy pyridine **10**, and 3-formyl-5-benzyloxy pyridine **11**<sup>14a,b</sup> are known compounds.

**2-Bromo-5-mesyloxy pyridine (3).** To a solution of 2-bromo-5-hydroxypyridine (**1**) (0.3 g, 1.72 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL), Et<sub>3</sub>N (1.19 mL, 8.62 mmol) was added. The mixture was cooled at 0 °C and MsCl (0.4 mL, 5.17 mmol) was added dropwise under stirring and then pyridine (0.15 mL, 1.72 mmol). The reaction mixture was stirred for 4 h at rt and then poured into ice water, neutralized with saturated aqueous solution of NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The solvent was removed under reduced pressure and the residue (0.52 g) was purified by column chromatography on silica gel. Elution with hexane-CH<sub>2</sub>Cl<sub>2</sub> (2:1) gave the mesyloxy pyridine **3** (0.433 g, 99%) as colourless prisms; mp 87.5-88.5 °C (Et<sub>2</sub>O). IR (KBr) cm<sup>-1</sup>: 1570, 1370. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 8.34 (dd, 1H, Py-H, *J* = 1.2; 2.1 Hz), 7.55 (d, 1H, Py-H, *J* = 1.2 Hz), 7.54 (d, 1H, Py-H, *J* = 2.1 Hz), 3.23 (s, 3H, CH<sub>3</sub>). LRMS (FAB, positive ion mode) *m/z* 252, 254 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>6</sub>H<sub>6</sub>BrNO<sub>3</sub>S: C, 28.59; H, 2.40; N, 5.56. Found C, 28.52; H, 2.38; N, 5.47.

**2-Bromo-4-formyl-5-tosyloxy pyridine (Ib).** To a LDA solution prepared from *n*-BuLi (hexane solution, 2 mL, 3.14 mmol) and *i*-Pr<sub>2</sub>NH (0.5 mL, 3.55 mmol) in Et<sub>2</sub>O (5 mL) at -80 °C for 1 h under Ar atmosphere, 2-bromo-5-tosyloxy pyridine **4** (0.1 g, 0.304 mmol) solved in dry Et<sub>2</sub>O (8 mL) was added slowly and the mixture was stirred for 1.5-2 h at -80 °C. Dry DMF (0.2 mL, 2.57 mmol) was added drop by drop. After 1 h of stirring at -80 °C, the mixture was hydrolyzed with a 10% degassed aqueous solution of KH<sub>2</sub>PO<sub>4</sub> (30 mL) and allowed to warm up to rt and extracted with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), evaporated and purified by column chromatography on silica gel. Elution with hexane-Et<sub>2</sub>O (5:1) gave the formylated product **Ib** (0.057 g, 53%) as colorless prisms, mp 105-107 °C (hexane-Et<sub>2</sub>O). IR (KBr) cm<sup>-1</sup>: 1700, 1590, 1380, 1180. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ: 10.04 (s, 1H, CHO), 8.11 (s, 1H, Py-H<sub>6</sub>), 7.86 (s, 1H, Py-H<sub>3</sub>), 7.73 (d, 2H, Ar-H, *J* = 8 Hz), 7.39 (d, 2H, Ar-H, *J* = 8 Hz), 2.49 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>) δ: 184.98 (CHO), 147.25 (C, C-Ar), 146.53 (CH, C<sub>6</sub>-Py), 145.26 (C, C<sub>2</sub>-Py), 140.49 (C, C<sub>5</sub>-Py), 136.84 (C, C<sub>4</sub>-Py), 130.49 (CH, 2C-Ar), 130.26 (C, C-Ar), 128.62 (CH, 2C-Ar), 125.77 (CH, C<sub>3</sub>-Py), 21.82 (CH<sub>3</sub>). MS (FAB, positive ion mode) *m/z* 356, 358 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>13</sub>H<sub>10</sub>BrNO<sub>4</sub>S: C, 43.84; H, 2.83; N, 3.93. Found: C, 44.19; H, 3.04; N, 3.79.

**2-Bromo-5-hydroxy-*N*-benzylpyridinium bromide (5).** To a solution of pyridine **1** (0.25 g, 1.43 mmol) in toluene (70 mL), BnBr (0.17 mL, 1.43 mmol) was added and the mixture was heated under reflux for 70 h. The solvent was removed under reduced pressure to furnish 2-bromo-5-hydroxy-*N*-benzylpyridinium bromide (**5**) (0.283 g, 56%) as white powder after washing with cold Et<sub>2</sub>O. mp 190-194 °C (EtOH). IR (KBr) cm<sup>-1</sup>: 3440, 3070, 1610, 1495, 1320. <sup>1</sup>H-NMR (300 MHz, DMSO) δ: 12.18 (s, 1H, OH), 8.91 (d, 1H, Py-H, *J* = 2.8 Hz), 8.27 (d, 1H, Py-H, *J* = 9.1 Hz), 7.90 (dd, 1H, Py-H, *J* = 2.8; 9.1 Hz), 7.43-7.26 (m, 5H, Ph-H), 5.91 (s, 2H, CH<sub>2</sub>-Ph). LRMS (M-Br)<sup>+</sup> 264, 266. Anal. Calcd for C<sub>12</sub>H<sub>11</sub>Br<sub>2</sub>NO: C, 41.77; H, 3.21; N, 4.06. Found: C, 42.03; H, 3.34; N 3.97.

**2-Bromo-5-benzyloxy-*N*-benzylpyridinium bromide (6).** To a solution of pyridine **2** (1 g, 3.78 mmol) in toluene (70 mL), BnBr (0.67 mL, 5.68 mmol) was added and the mixture was heated under reflux for 66 h. The solvent was removed and a liquid residue which crystallized in time was obtained. The crystals were filtered and washed with cold Et<sub>2</sub>O, giving the product **6** (0.982 g, 57%) as colourless cubic crystals. mp 142-144 °C (EtOH). IR (KBr) cm<sup>-1</sup>: 3060, 1615, 1510, 1260. <sup>1</sup>H-NMR (300 MHz, DMSO) δ: 9.45 (d, 1H, Py-H, *J* = 3 Hz), 8.46 (d, 1H, Py-H, *J* = 9.3 Hz), 8.31 (dd, 1H, Py-H, *J* = 3; 9.3 Hz), 7.52-7.28 (m, 10H, Ph-H), 5.97 (s, 2H, N-CH<sub>2</sub>-Ph), 5.39 (s, 2H, O-CH<sub>2</sub>-Ph). LRMS (M-Br)<sup>+</sup> 354, 356. Anal. Calcd for C<sub>19</sub>H<sub>17</sub>Br<sub>2</sub>NO: C, 52.44; H, 3.94; N, 3.22 Found C, 52.28; H, 4.01; N, 3.55.

**3-Benzyloxy-*N*-benzyl-1,2,5,6-tetrahydropyridine (8).** To a solution of *N*-benzylpyridinium bromide **6** (0.05g, 0.11 mmol) in dry MeOH (10 mL), NaBH<sub>3</sub>CN (0.014 g, 0.22 mmol) was added and the mixture was stirred for 22 h at rt. The mixture was poured into cold water, basified with saturated aqueous solution of NaHCO<sub>3</sub> and extracted with AcOEt. The combined organic extracts were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated. The residue (0.05 g), purified by column chromatography on silica gel (hexane-AcOEt 15:1) gave the tetrahydropyridine **8** (0.021 g, 65%) as pale yellow oil. IR (NaCl) cm<sup>-1</sup>: 3050, 1680, 1500, 1450, 1220, 1180. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.39-7.28 (m, 10H, Ph-H), 4.79 (t, 1H, Py-H, *J* = 3.7 Hz), 4.72 (s, 2H, O-CH<sub>2</sub>-Ph), 3.66 (s, 2H, N-CH<sub>2</sub>-Ph), 3.03 (d, 2H, Py-H, *J* = 0.9 Hz), 2.60 (t, 2H, Py-H, *J* = 5.8 Hz), 2.52-2.24 (m, 2H, Py-H). LRMS (FAB, positive ion mode) *m/z* 280 (M+H)<sup>+</sup>. HRMS (FAB) calcd for C<sub>19</sub>H<sub>22</sub>NO<sup>+</sup>: 280.1701, found 280.1708 (M+H)<sup>+</sup>.

**5-Benzyloxy-3-acetal pyridine (12).** 3-Formyl-5-benzyloxy-*N*-benzylpyridine (**11**) (0.27 g, 1.28 mmol) was dissolved in 25 mL of dry toluene. *p*-TsOH monohydrate (0.30 g, 1.6 mmol) was added and the mixture was stirred at 90 °C for 15 min. Ethylene glycol (0.35 mL, 6.29 mmol) was added and stirring was continued for 5 h at 110 °C. After the reaction was completed (TLC), the reaction mixture was cooled down, treated with saturated aqueous solution of NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were washed with brine, dried over anhydrous K<sub>2</sub>CO<sub>3</sub> and evaporated. The yellow liquid residue (0.49 g) was purified by column chromatography on silica gel (hexane-AcOEt 2:1) to give the acetal **12** (0.297 g, 90%) as a colourless oil which crystallized in time as white prisms. mp 37-39 °C (crude). IR (KBr) cm<sup>-1</sup>: 2845, 1590, 1460, 1290, 970. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 8.38 (d, 1H, Py-H, *J* = 3 Hz), 8.32 (d, 1H, Py-H, *J* = 1.2 Hz), 7.45-7.32 (m, 6H, Ar-H, Py-H), 5.84 (s, 1H, CH-acetal), 5.11 (s, 2H, O-CH<sub>2</sub>-Ph), 4.13-4.01 (m, 4H, O-CH<sub>2</sub>-CH<sub>2</sub>-O). LRMS (FAB, positive ion mode) *m/z* 258 (M+H)<sup>+</sup>. HRMS (FAB) calcd for C<sub>15</sub>H<sub>16</sub>NO<sub>3</sub><sup>+</sup>: 258.1130, found 258.1134 (M+H)<sup>+</sup>.

**5-(1,3-Dioxolan-2-yl)pyridin-3-ol (13).** A solution of pyridine **12** (0.61 g, 2.39 mmol) and 10% Pd on C (0.101 g) in MeOH (100 mL) was hydrogenated for 27 h at rt. The reaction mixture was filtered, washed through with MeOH and the filtrate was concentrated under reduced pressure to afford the compound **13** (0.393 g, 98%) as colourless prisms. mp 142-145 °C (CHCl<sub>3</sub>). IR (KBr) cm<sup>-1</sup>: 2845, 2810-2300, 1595,

1460, 1190, 970. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 8.23 (d, 1H, Py-H, *J* = 2.7 Hz), 8.21 (d, 1H, Py-H, *J* = 1.8 Hz), 7.39-7.38 (m, 1H, Py-H), 5.84 (s, 1H, CH-acetal), 4.13-4.08 (m, 2H, O-CH<sub>2</sub>-CH<sub>2</sub>-O), 4.06-4.01 (m, 2H, O-CH<sub>2</sub>-CH<sub>2</sub>-O). LRMS (FAB, positive ion mode) *m/z* 168 (M+H)<sup>+</sup>. *Anal.* Calcd for C<sub>8</sub>H<sub>9</sub>NO<sub>3</sub>: C, 57.48; H 5.43; N, 8.38; Found C, 57.14; H, 5.20; N, 8.27.

**2,4,6-Tribromo-5-(1,3-dioxolan-2-yl)pyridin-3-ol (14).** To a solution of pyridin-3-ol **13** (0.16 g, 0.99 mmol) in CH<sub>2</sub>Cl<sub>2</sub>-MeOH (20 mL-9 mL), dry Et<sub>3</sub>N (0.9 mL, 5.95 mmol) was added and the reaction mixture was stirred for a few minutes at -50 °C. After that BTMABr<sub>3</sub> (1.54 g, 3.97 mmol) solved in 20 mL of CH<sub>2</sub>Cl<sub>2</sub> was added dropwise. The temperature was increased from -50 °C to -35 °C during 3 h, after that 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with brine, dried (anhydrous K<sub>2</sub>CO<sub>3</sub>) and evaporated and the residue purified by column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>-MeOH 50:1) gave the tribromopyridine **14** (0.273 g, 68%) as a white powder. mp 192.5-193.5 °C (CHCl<sub>3</sub>). IR (KBr) cm<sup>-1</sup>: 3400-3200, 2845, 1540, 1430, 1160, 960. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 6.25 (s, 1H, CH-acetal), 4.35-4.27 (m, 2H, O-CH<sub>2</sub>-CH<sub>2</sub>-O), 4.16-4.08 (m, 2H, O-CH<sub>2</sub>-CH<sub>2</sub>-O). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ: 144.64 (C), 128.58 (C), 127.21 (C), 125.72 (C), 119.04 (C), 100.45 (CH), 62.96 (2C, CH<sub>2</sub>). LRMS (FAB, positive ion mode) *m/z* 402, 404, 406, 408 (M+H)<sup>+</sup>. *Anal.* Calcd for C<sub>8</sub>H<sub>6</sub>Br<sub>3</sub>NO<sub>3</sub>: C, 23.79; H, 1.50; N, 3.47; Found C, 23.75; H, 1.44; N, 3.32.

**3-Benzyloxy-2,4,6-tribromo-5-(1,3-dioxolan-2-yl)pyridine (15).** To a solution of tribromopyridine **14** (0.68 g, 1.7 mmol) in dry DMF (70 mL) at 0 °C, anhydrous K<sub>2</sub>CO<sub>3</sub> (0.47 g, 3.4 mmol) and a catalytic amount of KI (0.1 g) were added. The reaction mixture was stirred for 30 min at 0 °C and for another 30 min at rt, then was treated with BnBr (0.58 g, 3.4 mmol) for 6 h at rt. When the reaction was completed, cold water was added and the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and dried over anhydrous K<sub>2</sub>CO<sub>3</sub>. The solvent was removed under reduced pressure and the red liquid residue (1.52 g) was purified by column chromatography on silica gel (hexane-AcOEt 10:1) to give the benzyloxypyridine **15** (0.701 g, 84%) as colourless oil. IR (KBr) cm<sup>-1</sup>: 2860, 1520, 1420, 1220, 1030, 965. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.59-7.53 (m, 2H, Ar-H), 7.46-7.38 (m, 3H, Ar-H), 6.30 (s, 1H, CH-acetal), 5.05 (s, 2H, CH<sub>2</sub>Ph), 4.37-4.32 (m, 2H, O-CH<sub>2</sub>-CH<sub>2</sub>-O), 4.12-4.08 (m, 2H, O-CH<sub>2</sub>-CH<sub>2</sub>-O). LRMS (FAB, positive ion mode) *m/z* 492, 494, 496, 498 (M+H)<sup>+</sup>. HRMS (FAB) calcd for C<sub>15</sub>H<sub>13</sub>Br<sub>3</sub>NO<sub>3</sub><sup>+</sup>: 495.8352, found 495.8385 (M+H)<sup>+</sup>.

**5-Benzyloxy-2,4,6-tribromo-3-formylpyridine (1a).** To a solution of acetal **15** (0.74 g, 1.49 mmol) in THF (70 mL) was added 10% HCl (50 mL) and the reaction mixture was stirred for 3.5 h at 65 °C. After the reaction was completed (TLC), saturated aqueous solution of NaHCO<sub>3</sub> was added and the mixture was extracted with AcOEt. The combined organic extracts were washed with brine, dried over anhydrous K<sub>2</sub>CO<sub>3</sub> and evaporated under reduced pressure. The solid residue was purified by column chromatography on silica gel (hexane-AcOEt 20:1) to give the formylpyridine **1a** (0.58 g, 86%) as

colourless needles. mp 122.5-125 °C (Et<sub>2</sub>O-hexane). IR (KBr) cm<sup>-1</sup>: 1700, 1525, 1500, 1220, 1030. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 10.17 (s, 1H, CHO), 7.58-7.52 (m, 2H, Ar-H), 7.44-7.41 (m, 3H, Ar-H), 5.10 (s, 2H, CH<sub>2</sub>Ph). LRMS (FAB, positive ion mode) *m/z* 448, 450, 452, 454 (M+H)<sup>+</sup>. *Anal.* Calcd for C<sub>13</sub>H<sub>8</sub>Br<sub>3</sub>NO<sub>2</sub>: C, 34.70; H 1.79; N, 3.11. Found C, 34.93; H, 1.81; N, 3.07.

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