# Efficient Regioselective Preparation of Monobromo and Bromoiodo Hydroxy Pyridines from Dibromoderivatives via Bromine-Lithium Exchange

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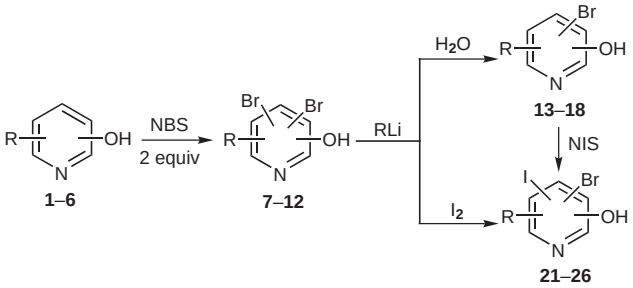
**Abstract:** Annular dibromination of hydroxypyridines with NBS in acetonitrile followed by bromine-lithium exchange with RLi and subsequent trapping with $H_2O$ or $I_2$ afforded monobromo and bromoiodo derivatives in a completely regioselective way. Iodination of bromo hydroxypyridines with NIS is totally regioselective.

**Key words:** hydroxypyridines, bromine-lithium exchange, *N*-bromosuccinimide, *N*-iodosuccinimide, bromoiodo pyridines

Polyfunctional pyridines have become essential in many fields, such as pharmaceutical chemistry,[1] transition metal chemistry,[2] optoelectronic[3] or luminescent materials[4] and in supramolecular chemistry.[5] Bromo and iodopyridines appear as particularly useful key intermediates for synthesis since they easily undergo regioselective deprotonation,[6] halogen-metal exchange,[7,8] nucleophilic substitutions,[9] and oxidative additions with Pd(0).[10] Therefore, the search of new regioselective methods affording halopyridines is a matter of great interest.

The most direct approach to obtain halopyridines is the electrophilic halogenation starting from the corresponding activated pyridines. In this way $Br_2$ and $I_2$ have been employed for the highly regioselective bromination and iodination of 3-hydroxypyridines.[11] The usefulness of NBS in the halogenation of activated aromatic carbocycles has been reported by our group.[12] We have also recently reported that NBS in MeCN allows the highly regioselective monobromination of 2-hydroxypyridine (**1**),[13] but the method is not successful starting from 4-hydroxypyridine (**2**) and for methyl hydroxypyridines.[14]

Considering that compounds **1** and **2** could be easily dibrominated by using 2 equivalents of NBS,[13] and taking into account that regioselective monolithiation of unsubstituted dibromopyridines had been reported by several authors,[7a–c,7e] we decided to investigate the regioselectivity of the metal-halogen interchange on dibromo hydroxypyridines as a tool for the regioselective introduction of any electrophile in the hydroxypyridine rings. Moreover, the knowledge of the role of the oxygenated function in modulating the strong regioselectivity control imposed by the pyridine ring could also be important. In this paper we report the reactions with $H^+$ and $I_2$ as electrophiles to obtain monobromo and bromoiodo hydroxypyridines in a completely regioselective way. All the studied compounds are commercially available. The strategy developed is based on a two-step sequence involving (i) regioselective annular dibromination with NBS of hydroxypyridines **1**–**6** and (ii) regioselective bromine-lithium exchange of the resulting dibromo derivatives followed by capture with of $H_2O$ or $I_2$ as the electrophiles (Scheme 1). Alternatively, the synthesis of bromoiodo derivatives have been carried out by reaction of monobromo pyridines with *N*-iodosuccinimide, NIS.




**Scheme 1**

Dibromination of 2-hydroxy and 4-hydroxy pyridines (**1** and **2**) with NBS in $CCl_4$ had been previously reported.[13] Similar results were obtained from the hydroxypyridines **3**–**6** when they were treated with NBS (2 equiv) in MeCN (Table 1).

After 1 hour at reflux, all the substrates evolved into the dibrominated products[15] on the positions activated by the OH group in a very high yields (>86% isolated yields). The formation of the chain halogenation products was not detected. Succinimide, the only by-product of these reactions, can be easily removed by successive washing with MeOH from the reaction crudes containing **7**, **9** and **10**. As compounds **8**, **11** and **12** are soluble in MeOH, they had to be purified by chromatography.

With dibromopyridines in hand, the regioselectivity of the bromine-lithium exchange was then investigated. In a first attempt we carried out metallation of the sodium salt of the substrate (formed in situ by addition of 1.2 equiv of NaH at room temperature) with 1 equivalent of *n*-BuLi, at –78 °C.[16] Nevertheless, more than 30% of the unaltered starting product (**7**–**12**) was recovered after long periods

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Art Id.1437-2096,E;2003,0,11,1678,1682,ftx,en;D15103ST.pdf.
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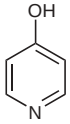
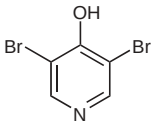
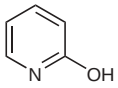
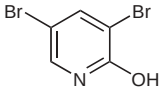
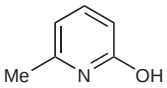
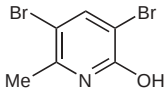
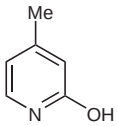
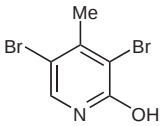
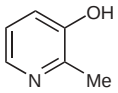
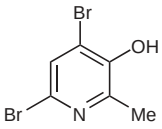
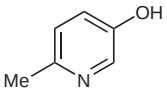
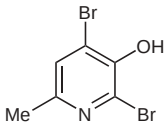
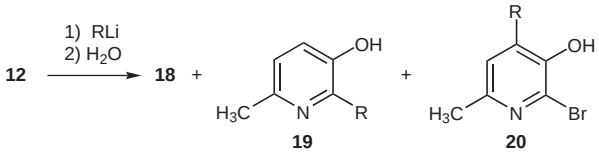
**Table 1** Annular Dibromination of compounds **1**–**6** with NBS/ MeCN

| Entry | Substrate | Product | % Yield[a] |
|---|---|---|---|
| 1 |  **2** |  **7** | 95[13] |
| 2 |  **1** |  **8** | 95[13] |
| 3 |  **3** |  **9** | 89 |
| 4 |  **4** |  **10** | 87 |
| 5 |  **5** |  **11** | 90 |
| 6 |  **6** |  **12** | 86 |

[a] Isolated yield.

of time. The alternative bromine-lithium exchange performed at –90 ºC by reaction of the *O*-lithium salts (formed with 1 equiv of the organollithium) with RLi gave better results. Various RLi were tested in order to optimize the exchange conditions on the dibromopyridines. It was found that *n*-BuLi was the best exchange reagent, except for **8** which reacted better with *s*-BuLi (Table 2). The bulky *t*-BuLi did not give satisfactory results. When the lithio derivative was treated with water (10 equiv) only the monobromo derivatives **13**–**18**[17] were obtained in all the examples. It is important to remark that no lithiation of the methyl group[18] was observed for methyl pyridines **9**–**12**, but dilithium-bromine exchange occured for **7**, **8**, and **10**, thus affording totally debrominated pyridines in 30%, 9%, and 30% yields, respectively (Table 2, entries 1, 2 and 4). This result could not be avoided by using 1 equivalent of *n*-BuLi, or by inverting the addition mode according to the method of Cai,[7b] which afforded poor yields of monobromo pyridines. In $CH_2Cl_2$[7c] no reaction was observed probably due to the poor solubility of hydroxypyridines in this solvent. Compound **12** evolved into a mixture of **18** with 2-alkyl-3-hydroxy-6-methyl pyridine (**19**) and 4-alkyl-2-bromo-3-hydroxy-6-methylpyridine (**20**), as a result of the nucleophilic substitution of each bromine atoms in dibromoderivative **12**, by the alkyl group. The **18:19:20** ratios varied with the size of the alkyl group (55:25:20 for *n*-BuLi, 45:44:11 for *s*-BuLi and 10:70:20 for *t*-BuLi) (Scheme 2).



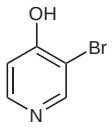
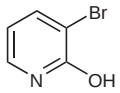
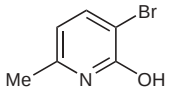
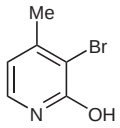
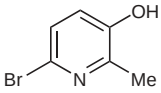
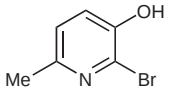
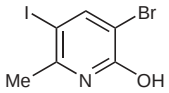
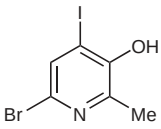

**Scheme 2**

To the best of our knowledge the herein reported method is the first allowing the regioselective preparation of 3-bromo-4-pyridone, **13**. For 3,5-dibromo-2-hydroxy pyridines **8**, **9**, and **10** lithiation took place regioselectively at C-5 position to afford 3-bromo derivatives (Table 2, entries 2–4) that are not available by electrophilic aromatic substitution of the corresponding hydroxy pyridines. The regioselectivity of this bromine-lithium exchange is just the opposite and therefore complementary, to that reported for 3,5-dibromo-2-methoxy pyridine,[19,20] which could be due to the low stability of the carbanions at *ortho* position with respect to the pyridinolate anion. Despite this fact, the reaction of the 3-hydroxy pyridine (**11**) only afforded compound **17**, resulting from the monodebromination at one *ortho* position, C-4. This result suggests the formation of the carbanions at C-6 is even less favored, which could be due to the strong electronic repulsion of the lone electron pairs at two contiguous atoms (C-6 and N). This could also account for the evolution of compound **12**, which is unexpectedly prone to the nucleophilic substitution instead of the bromine-lithium exchange (the carbanion at C-2 would be highly unstable).

The intermediates derived from **9** and **11**, which quantitatively evolved into the monobromoderivatives, were also captured by using $I_2$ as the electrophile (entries 7 and 8, Table 2). As we can see, the iodination was also completely regioselective, only affording bromoiodo derivatives **21** and **22**[20] in high yields.

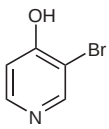
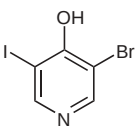
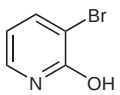
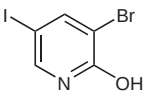
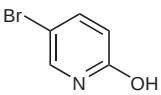
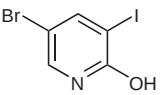
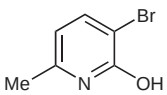
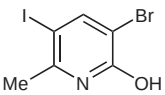
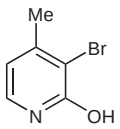
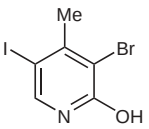
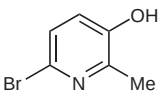
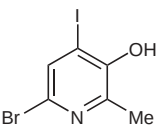
Since the preparation of bromoiodopyridines only proceeds successfully with those substrates that undergo clean monolithiation, and these compounds are highly interesting for the sequential introduction of two different groups at the pyridine ring, we decided to study the ability of the *N*-iodosuccinimide in the regiocontrolled iodination of monobromo hydroxypyridines. Compounds **13**–**17** (Table 2) and 5-bromo-2-hydroxypyridine (**27**), which had been obtained in the direct regioselective monobromination of 2-hydroxy pyridine,[13] reacted with NIS in MeCN at reflux (Table 3) to afford exclusively the products of the completely regioselective iodination of the pyridine ring at the position activated by the hydroxy group.[20]

**Table 2** Regioselective Bromine-Lithium Exchange of Dibromo Hydroxypyridines **7**–**12**

| Entry | Subst. | RLi | E | Product | % Ratio (yield)[a] |
|---|---|---|---|---|---|
| 1 | **7** | *n*-BuLi | $H_2O$ |  **13** | 70 (52) |
| 2 | **8** | *s*-BuLi | $H_2O$ |  **14** | 91 (71) |
| 3 | **9** | *n*-BuLi | $H_2O$ |  **15** | 100 (80) |
| 4 | **10** | *n*-BuLi | $H_2O$ |  **16** | 70 (50) |
| 5 | **11** | *n*-BuLi | $H_2O$ |  **17** | 100 (80) |
| 6 | **12** | *n*-BuLi | $H_2O$ |  **18** | 55 (35)[b] |
| 7 | **9** | *n*-BuLi | $I_2$ |  **21** | 100 (60) |
| 8 | **11** | *n*-BuLi | $I_2$ |  **22** | 100 (65) |

[a] Isolated yield.
[b] See text.

**Table 3** Annular Iodination of Bromo Hydroxypyridines with NIS in MeCN at Reflux

| Entry | Substrate | Time (h) | Product | % Yield[a] |
|---|---|---|---|---|
| 1 |  **13** | 1 |  **23** | 89 |
| 2 |  **14** | 1 |  **24** | 92 |
| 3 |  **27** | 1 |  **25** | 91 |
| 4 |  **15** | 1 |  **21** | 91 |
| 5 |  **16** | 1 |  **26** | 92 |
| 6 |  **17** | 4 |  **22** | 95 |

[a] Isolated yield.

As expected, iodination at C-4 of the pyridine ring (4 hours in refluxing acetonitrile; entry 6, Table 3) is slower than that at C-3 or C-5 (entries 1–5, Table 3). However, the yields are almost quantitative in all the cases (isolated yields are usually higher than 90%). Pure bromoiodo derivatives **21** and **23**–**25** can be easily isolated by washing the reaction crude with methanol, thus removing NHS. Derivatives **22** and **26** were purified by column chromatography. As it had been found with NBS, chain iodination products were not detected in reactions from methyl derivatives.

In summary, dibromination of 4- and 2-hydroxypyridines and their subsequent bromine-lithium exchange are both completely regioselective.The hydrolysis of the intermediates provides a new entry to 3-bromohydroxy pyridines, not available by electrophilic aromatic substitution. The application of a similar sequence to 3-hydroxy methylpyridines is also completely regioselective, the reactivity order being C-4 > C-6 > C-2. The use of iodine as the electrophile in these reactions affords bromoiodo derivatives with total and identical regioselectivity, but the synthesis of these compounds can be achieved more efficiently by nuclear iodination of the bromo hydroxypyridines with NIS in MeCN. The use of both monobromo and bromoiodo hydroxypyridines with different electrophiles is currently under study.

## References


(1) (a) Sharples, C. G. V.; Karig, G.; Simpson, G. L.; Spencer, J. A.; Wright, E.; Millar, N. S.; Wonnacott, S.; Gallagher, T. *J. Med. Chem.* **2002**, *45*, 3235. (b) Enyedy, I. J.; Sakamury, S.; Zaman, W. A.; Johnson, K. M.; Wang, S. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 513. (c) Raulee, I.; Sivakumar, R.; Muruganantham, N.; Anbalagan, N.; Gunasekaran, V.; Leonard, J. T. *Chem. Pharm. Bull.* **2003**, *51*, 162. (d) For agrochemical compounds see: Yano, T.; Okano, N.; Ugai, S.; Hori, M.; Hirai, K. *J. Pesticide Sci.* **2001**, *26*, 67. (e) Also see: Fhu, J. B.; Wang, M. G.; Wu, W. J.; Ji, Z. Q.; Hu, Z. N. *Phytochemistry* **2002**, *61*, 699.

(2) (a) Kaes, C.; Katz, A.; Hosseini, M. W. *Chem. Rev.* **2000**, *100*, 3553. (b) Heller, M.; Shubert, U. S. *J. Org. Chem.* **2002**, *67*, 8269. (c) Bera, J. K.; Dunbar, K. R. *Angew. Chem. Int. Ed.* **2002**, *41*, 4453.

(3) (a) Le Bozec, H.; Renouard, T. *Eur. J. Inorg. Chem.* **2000**, *2*, 229. (b) Skaff, H.; Emrick, T. *Chem. Commun.* **2003**, 52. (c) Tessore, F.; Roberto, D.; Ugo, R.; Mussini, P.; Quici, S.; Ledoux-Rak, J.; Zyss, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 456.

(4) (a) O'Regan, B.; Grätzel, M. *Nature (London)* **1991**, *353*, 737. (b) Vitale, M.; Ford, P. C. *Coord. Chem. Rev.* **2001**, *219*, 3. (c) Muramatsu, Y.; Yamamoto, T.; Hayakawa, T.; Koinuma, H. *Appl. Surf. Sci.* **2002**, *189*, 319.

(5) (a) Constable, E. C. In *Progress in Inorganic Chemistry*, Vol. 42; Karlin, K. D., Ed.; Wiley: NewYork, **1994**, 67. (b) Hanan, G.; Schubert, U.; Volkmer, D.; Riviere, E.; Lehn, J.-M.; Kyritaska, N.; Fischer, J. *Can. J. Chem.* **1997**, *75*, 169.

(6) Some reviews: (a) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059. (b) Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2002**, 3375. (c) Karig, G.; Thasana, N.; Gallagher, T. *Synlett* **2002**, 808. (d) Lazaar, J.; Rebstock, A.; Mongin, F.; Godard, A.; Trécourt, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2002**, *58*, 6723.

(7) For RLi see: (a) Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485. (b) Cai, D.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett.* **1996**, *37*, 2537. (c) Peterson, M. A.; Mitchell, J. R. *J. Org. Chem.* **1997**, *62*, 8237. (d) Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 4285. (e) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885. (f) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323. (g) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369.

(8) For RMgX see: (a) Bérillon, L.; Leprête, A.; Turck, A.; Plé, N.; Quéguiner, G.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 1359. (b) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349. (c) Cai, W.; Ripin, D. H. *Synlett* **2002**, 273. (d) Kato, S.; Nonoyama, N.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2002**, 7315. (e) Schlosser, M.; Cottet, F. *Eur. J. Org. Chem.* **2002**, 4181.

(9) (a) Skerlj, R. T.; Bogucki, D.; Bridger, G. J. *Synlett* **2000**, 1488. (b) Cherng, Y.-J. *Tetrahedron* **2002**, *58*, 4931.

(10) For bromopyridines see: (a) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron Lett.* **2001**, *42*, 5717. (b) Iglesias, B.; Alvárez, R.; Lera, A. R. *Tetrahedron* **2001**, *57*, 3125. (c) Alami, M.; Peyrat, J.-F.; Belachmi, L.; Brion, J.-D. *Eur. J. Org. Chem.* **2001**, 4270. (d) Zhang, N.; Thomas, L.; Wu, B. *J. Org. Chem.* **2001**, *66*, 1500. (e) Morris, G. A.; Nguyen, S. T. *Tetrahedron Lett.* **2001**, *42*, 2093. (f) Bonnaite, S. C.; Carpentier, J.-F.; Mortreux, A.; Castanet, Y. *Tetrahedron Lett.* **2001**, *42*, 3689. (g) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron* **2002**, *58*, 4429. (h) For iodopyridines see: Mello, J. V.; Finney, N. S. *Org. Lett.* **2001**, *3*, 4263. (i) See also: Phuan, P.-W.; Kozlowski, M. C. *Tetrahedron Lett.* **2001**, *42*, 3963. (j) See also: Yue, W. S.; Li, J. K. *Org. Lett.* **2002**, *4*, 2201.

(11) Schanatterer, S.; Koch, V. *Synthesis* **1990**, 497.

(12) (a) Carreño, M. C.; García Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328. (b) Carreño, M. C.; García Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. *Tetrahedron. Lett.* **1996**, *37*, 4081. (c) Carreño, M. C.; García Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. *Synlett* **1997**, 1241.

(13) Cañibano, V.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; Carreño, M. C.; González, G.; García-Ruano, J. L. *Synthesis* **2001**, 2175.

(14) Unpublished results. Bromination of methyl hydroxy-pyridines **3**–**6** were carried out with 1 equivalent of NBS in acetonitrile. For **3**, 3-bromo-, 5-bromo- and 3,5-dibromo 2-hydroxy-6-methyl pyridines were formed in a 28:54:9 ratio. For **4**, 3-bromo-, 5-bromo- and 3,5-dibromo 2-hydroxy-4-methyl pyridines were formed in a 36:44:8 ratio. For **5**, 6-bromo- and 4,6-dibromo 3-hydroxy-2-methyl pyridines were formed in a 20:40 ratio. For **6** 2-bromo- and 2,4-dibromo 3-hydroxy-6-methyl pyridines were formed in a 23:38 ratio. The rest up to 100% were unaltered starting material.

(15) Dibromopyridines **9**–**12** were characterized on the basis of their $^1$H NMR (δ in ppm, DMSO-$d_6$, 300 MHz) and $^{13}$C NMR (δ in ppm, DMSO-$d_6$, 75 MHz) spectroscopic data and elemental analysis.
Compound **9**: white solid; mp 223–224 °C ($Et_2O$/hexane); $^1$H NMR: 2.23 (s, 3 H, $CH_3$), 8.04 (s, 1 H, H-C4), 12.50 (br s, 1 H, OH); $^{13}$C NMR: 19.2 ($CH_3$), 97.0 (C-5), 112.3 (C-3), 144.8 (C-4), 145.7 (C-6), 158.3 (C-2); Anal. Calcd for $C_6H_5NOBr_2$: C, 27.00; H, 1.89; N, 5.25. Found: C, 27.44; H, 1.98; N, 5.29.
Compound **10**: white solid; mp 222–223 °C (methanol); $^1$H NMR: 2.41 (s, 3 H, $CH_3$), 7.76 (s, 1 H, H-C6), 12.29 (br s, 1 H, OH); $^{13}$C NMR: 24.1 ($CH_3$), 100.5 (C-5), 116.7 (C-3), 135.0 (C-6), 149.3 (C-4), 157.7 (C-2); Anal. Calcd. for $C_6H_5NOBr_2$: C, 27.00; H, 1.89; N, 5.25. Found: C, 27.08; H, 1.95; N, 5.37.
Compound **11**: yellow solid; mp 107–108 °C ($Et_2O$/hexane); $^1$H NMR: 2.39 (s, 3 H, $CH_3$), 7.68 (s, 1 H, H-C5), 9.98 (br s, 1 H, OH); $^{13}$C NMR: 19.9 ($CH_3$), 122.4 (C-4), 128.4 (C-5), 128.6 (C-6), 148.8 and 149.1 (C-2 and C-3); Anal. Calcd for $C_6H_5NOBr_2$: C, 27.00; H, 1.89; N, 5.25. Found: C, 27.24; H, 2.02; N, 5.34.
Compound **12**: yellow solid; mp 100–101°C ($Et_2O$/hexane); $^1$H NMR (DMSO-$d_6$): 2.33 (s, 3 H, $CH_3$), 7.52 (s, 1 H, H-C5), 10.30 (br s, 1 H, OH); $^{13}$C NMR (DMSO-$d_6$): 22.2 ($CH_3$), 121.9 (C-4), 127.2 (C-5), 131.3 (C-2), 146.3 (C-6), 150.6 (C-3). Anal. Calcd for $C_6H_5NOBr_2$: C, 27.00; H, 1.89; N, 5.25. Found: C, 27.44; H, 2.03; N, 5.34.

(16) Mongin, F.; Fourquez, J.-M.; Rault, S.; Levacher, V.; Godard, A.; Trécourt, F.; Quéguiner, G. *Tetrahedron Lett.* **1995**, *36*, 8415.

(17) Compounds **13** and **14** had been previously reported.[13] Monobromo hydroxypyridines **15**–**18** were characterized on the basis of their $^1$H NMR (δ in ppm, 300 MHz) and $^{13}$C NMR (δ in ppm, 75 MHz) spectroscopic data and elemental analysis.
Compound **15**: white solid; mp 220–221 °C ($Et_2O$/hexane); $^1$H NMR ($CDCl_3$): 2.38 (s, 3 H, $CH_3$), 6.00 (d, 1 H, $J_{5,4}$ = 7.5 Hz, H-C5), 7.72 (d, 1 H, $J_{4,5}$ = 7.5 Hz, H-C4), 13.24 (br s, 1 H, OH); $^{13}$C NMR ($CDCl_3$): 18.9 ($CH_3$), 106.7 (C-5), 111.2 (C-3), 143.7 (C-4), 145.8 (C-6), 161.7 (C-2); Anal. Calcd for $C_6H_6NOBr$: C, 38.32; H, 3.22; N, 7.45. Found: C, 38.52; H, 3.18; N, 7.45.
Compound **16**: white solid; mp 195–196 °C (acetone); $^1$H NMR (DMSO-$d_6$): 2.25 (s, 3 H, C$H_3$), 6.19 (d, 1 H, $J_{5,6}$ = 6.5 Hz, H-C5), 7.32 (d, 1 H, $J_{6,5}$ = 6.5 Hz, H-C6), 11.90 (br s, 1 H, OH); $^{13}$C NMR (DMSO-$d_6$): 23.1 ($CH_3$), 107.9 (C-5), 116.0 (C-3), 133.0 (C-6), 151.1 (C-4), 158.4 (C-2); Anal. Calcd for $C_6H_6NOBr$: C, 38.32; H, 3.22; N, 7.45. Found: C, 38.37; H, 3.22; N, 7.54.
Compound **17**: white solid; mp 199–200 °C ($Et_2O$/hexane); $^1$H NMR ($CDCl_3$): 2.42 (s, 3 H, C**H**$_3$), 7.00 (d, 1 H, $J_{4,5}$ = 8.4 Hz, H-C4), 7.09 (d, 1 H, $J_{5,4}$ = 8.4 Hz, H-C5), 9.01 (br s, 1 H, OH); $^{13}$C NMR ($CDCl_3$): 18.7 ($CH_3$), 124.8 and 125.7 (C-4 and C-5), 128.0 (C-6), 147.5 (C-2), 151.4 (C-3). HRMS (EI) calcd for $C_6H_6NOBr$: 186.9632. Found 186.9629.
Compound **18**: white solid; $^1$H NMR (DMSO-$d_6$): 2.31 (s, 3 H, $CH_3$), 7.05 (d, 1 H, $J_{4,5}$ = 8.1 Hz, H-C4), 7.15 (d, 1 H, $J_{5,4}$ = 8.1 Hz, H-C5); $^{13}$C NMR (DMSO-$d_6$): 22.4 ($CH_3$), 123.3 and 123.9 (C-5 and C-4), 129.0 (C-2), 148,6 and 148.7 (C-6 and C-3).

(18) For preference for ring lithiation over deprotonation see: Carpentier, T. A.; Jenner, P. J.; Leeper, F. J.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1980**, 1227.

(19) (a) Bargar, T. M.; Wilson, T.; Daniel, J. K. *J. Heterocycl. Chem.* **1985**, *22*, 1583. (b) Tee, O. S.; Paventi, M. *J. Am. Chem. Soc.* **1982**, *104*, 4142.

(20) Bromoiodo derivatives **21**–**26** were characterized on the basis of their $^1$H NMR (δ in ppm, 300 MHz) and $^{13}$C NMR (δ in ppm, 75 MHz) spectroscopic data and elemental analysis.
Compound **21**: yellow solid; mp 205–206 °C (acetone/methanol); $^1$H NMR ($CDCl_3$): 2.52 (s, 3 H, C$H_3$), 8.03 (s, 1H, H-C4), 13.47 (br s, 1 H, OH); $^{13}$C NMR ($CDCl_3$): 23.9 ($CH_3$), 68.9 (C-5), 112.4 (C-3), 147.4 (C-6), 151.2 (C-4), 161.3 (C-2). HRMS (EI) calcd. for $C_6H_5NOBrI$: 312.8599. Found: 312.8599.
Compound **22**: yellow solid; mp 115–116 °C(acetone); $^1$H NMR (DMSO-$d_6$): 2.38 (s, 3 H, $CH_3$), 7.78 (s, 1 H, H-C5), 9.85 (br s, 1 H, OH); $^{13}$C NMR (DMSO-$d_6$): 20.1 ($CH_3$), 100.9 (C-4), 129.2 (C-6), 134.1 (C-5), 147.2 (C-2), 151.5 (C-3). HRMS (EI) calcd for $C_6H_5NOBrI$: 312.8599. Found: 312.8603.
Compound **23**: yellow solid; $^1$H NMR (DMSO-$d_6$): 8.24 (d, 1 H, $J_{2,6}$ = 0.9 Hz, H-C2), 8.29 (d, 1 H, $J_{2,6}$ = 0.9 Hz, H-C6); $^{13}$C NMR (DMSO-$d_6$): 89.5 (C-5), 109.3 (C-3), 138.7 (C-2), 143.1 (C-6), 169.2 (C-4). HRMS (EI) calcd for $C_5H_3NOBrI$: 298.8442. Found 298.8434.
Compound **24**: yellow solid; mp 243–244 °C (acetone); $^1$H NMR (DMSO-$d_6$): 7.71 (d, 1 H, $J_{4,6}$ = 1.7 Hz, H-C4), 8.08 (d, 1 H, $J_{4,6}$ = 1.7 Hz, H-C6), 12.29 (br s, 1 H, OH); $^{13}$C NMR (DMSO-$d_6$): 64.3 (C-5), 116.4 (C-3), 140.7 (C-4), 148.8 (C-6), 157.5 (C-2). Anal Calcd. for $C_5H_3NOBrI$: C, 20.02; H, 1.01; N, 4.67. Found: C, 19.93; H, 1.02; N, 4.55.
Compound **25**: yellow solid; mp 226–227 °C(acetone); $^1$H NMR (DMSO-$d_6$): 7.74 (d, 1 H, $J_{4,6}$ = 2.4 Hz, H-C4), 8.21 (d, 1 H, $J_{4,6}$ = 2.4 Hz, H-C6), 12.23 (br s, 1 H, OH); $^{13}$C NMR (DMSO-$d_6$): 93.8 (C-5), 97.2 (C-3), 136.8 (C-4), 150.8 (C-6), 159.0 (C-2). Anal Calcd. for $C_5H_3NOBrI$: C, 20.02; H, 1.01; N, 4.67. Found: C, 19.90; H, 0.96; N, 4.57.
Compound **26**: yellow solid; mp 218–220 °C (acetone/methanol); $^1$H NMR (DMSO-$d_6$): 2.45 (s, 3 H, $CH_3$), 7.78 (s, 1 H, H-C6), 12.17 (br s, 1 H, OH); $^{13}$C NMR (DMSO-$d_6$): 29.1 ($CH_3$), 72.3 (C-5), 116.1 (C-3), 139.7 (C-6), 151.4 (C-4), 157.9 (C-2). HRMS (EI) calcd for $C_6H_5NOBrI$: 312.8599. Found: 312.8592.