A facile and efficient iodination of 5,6-di(arylamino)pyridine-2,3-diones

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A simple and efficient method for the iodination of 5,6-di(arylamino)pyridine-2,3-diones using iodine with ethanol at room temperature is described. Notable advantages include mild reaction condition, no need for a catalyst, short reaction time, simple practical procedure, giving excellent yield of the product. Iodopyridines have important medical applications as drug or diagnostic aids and radiolabelled compounds.

Keywords: iodination, iodine, pyridine-2,3-dione, aromatic-amine, radiolabelled compounds

Iodo substituents offer various functionalities because of their excellent reactivity.[1] The iodine may be replaced by lithium or magnesium, the organometallic intermediate may then be converted into a functionalised derivative by reaction with a suitable electrophile.[2–4] Consequently, substituents can be easily functionalised through cross-coupling reactions in the synthesis of many interesting natural products and bioactive material.[5,6] Iodopyridines are used in medicine as drug or diagnostic aids and radiolabelled compounds.[7] While iodopyridines are versatile intermediates, their limited commercial availability requires that they be synthesised from readily available precursors. One of the most common methods for the preparation of iodopyridines involves lithiation of activated pyridines followed by quenching with iodine.[8] The major disadvantage of this protocol is that sensitive functional groups are not well tolerated leading to either competing side reactions or decomposition of either the starting materials or products.[9] Therefore, the development of new, efficient synthetic method of iodopyridines is very important. We report here a facile and efficient protocol for the direct iodination of 5,6-di(arylamino)pyridine-2,3-diones with iodine (Scheme 1).

Results and discussion

The 4-iodo-5,6-5,6-di(arylamino)pyridine-2,3-diones **2** were synthesised by direct iodination of 5,6-di(arylamino)pyridine-2,3-diones **1** with iodine without a catalyst at room temperature. The intermediate product 5,6-di(arylamino)pyridine-2,3-diones were prepared by the Michael oxidation. where addition of aromatic amine with 3-hydroxypyridin-2(*1H*)-ones is carried out in the presence of oxidant $NaIO_3$ at room temperature. The reaction did not require catalysis and an excellent yield could be obtained. The structure of the formed products was supported based on the elemental analysis and spectral data (IR, NMR and MS). The IR spectrum of **2a** revealed the presence of two carbonyl stretching vibration bands at 1719 and 1655 cm^{-1}, the absorption peak at 3431 cm^{-1} indicated the presence of N-H stretching vibration. The mass spectrum of **2a** showed a molecular ion peak at *m/z* 446 ($[M+H]^+$), which indicated the addition of iodine to the 5,6-di(arylamino)pyridine-2,3-diones. The ^1H NMR spectrum of **2a** demonstrated the presence of a singlet of two methyl protons of benzene ring at δ 2.41, several multiplets in the range of δ 6.85–7.27 assigned as aromatic protons of benzene ring, and two singlets at δ 8.31 and 8.92 were assigned to the two NH respectively. An important characteristic feature in the 1H NMR spectra of **2a** was the disappearance of the signals at δ 5.93 for 4-H of pyridine ring, which was present in the spectra of the intermediate 5,6-di(*p*-methylanilino)pyridine-2,3-dione,[10] thus suggesting the iodination of compound **1** had taken place at the 4-position of the pyridine and not at the aromatic ring. The ^{13}C NMR spectrum of the product **2a** revealed the presence of two methyl carbons at δ 20.9 and 21.2, and two carbonyl carbons at δ 151.5 and. 171.0.

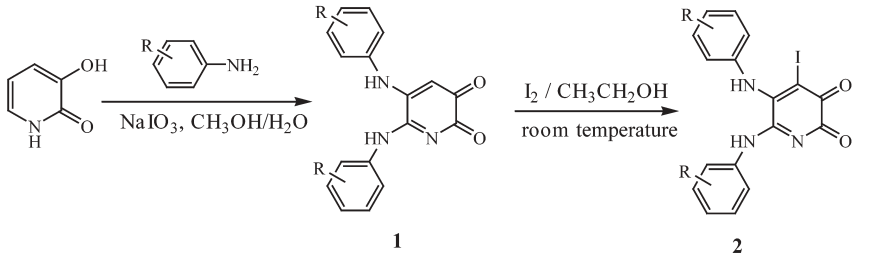
In conclusion, a simple and convenient method for the direct iodination of 5,6-di(arylamino)pyridine-2,3-diones has been developed. The major advantages of this method include no catalyst, mild conditions, simple operation and short reaction time with excellent yield.

Experimental

Melting points were determined in the open capillaries and were uncorrected. IR spectra were recorded on a PE-2000 spectrometer in KBr pellets and reported in cm^{-1}. All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for ^1H, and 125 MHz for ^{13}C, TMS was used as an internal reference for ^1H and ^{13}C chemical shifts and $CDCl_3$ was used as solvent. Mass spectra were collected on a Bruker ESQUIRE electrospray/ion trap instrument. Elemental analysis was determined with a Perkin-Elmer 240c elemental analysis instrument. All starting materials were commercial except 5,6-di(arylamino)pyridine-2,3-diones **1**, which was prepared according to a literature procedure.[10]

Iodination of 5,6-di(arylamino)pyridine-2,3-diones derivatives; general procedure

5,6-Di(arylamino)pyridine-2,3-diones compounds **1** (1 mmol) and iodine (0.305 g, 1.2 mmol) were dissolved in anhydrous ethanol



1 **2**

R= *p*-CH_3 *p*-Cl *p*-F *o*-CH_3O *m*-CH_3 *o*-CH_3 *m*-Cl *m*-CH_3O *p*-CH_3O

Scheme 1 Synthetic of 4-iodo-5,6-di(arylamino)pyridine-2,3-diones.

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(20 mL). The mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure to yield a crude solid. The obtained solid was dissolved in ethyl acetate (50 mL), washed by sodium thiosulfate (0.5 mol L^{-1}, 50 mL × 3), and then dried by anhydrous magnesium sulfate. The crude product is recrystallised from ethanol/acetone to afford the corresponding **2**.

4-Iodo-5,6-di(p-methylanilino)pyridine-2,3-dione (**2a**): Yield (87.5%); yellow powder, m.p. 123.6–125.4 °C. IR (KBr, cm^{-1}): 3431, 3214, 1719, 1655, 1574, 1507; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.41 (s, 6H, $2CH_3$), 6.85–7.27 (m, 8H, ArH), 8.31 (s, 1H, NH), 8.92 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.9, 21.2, 78.4, 120.3, 126.5, 129.3, 130.8, 133.4, 136.3, 137.1, 140.9, 141.0, 147.1, 151.5, 171.0; MS (ESI) *m/z* 446.3 $(M+H)^+$. Anal. Calcd for $C_{19}H_{16}IN_3O_2$: C, 51.25; H, 3.62; N, 9.44. Found: C, 51.53; H, 3.80; N, 9.59%.

4-Iodo-5,6-di(p-chloroanilino)pyridine-2,3-dione (**2b**): Yield (83.5%), red powder, m.p. 128.9–130.1 °C. IR (KBr, cm^{-1}): 3436, 3221, 1719, 1655, 1552, 1484; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.93 (d, J = 9 Hz, 2H, ArH), 7.13 (d, J = 8.5 Hz, 2H, ArH), 7.40 (d, J = 8.5 Hz, 2H, ArH), 7.45 (d, J = 8.0 Hz, 2H, ArH), 8.41 (s, 1H, NH), 8.78 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 79.6, 116.3, 122.0, 127.7, 128.9, 129.8, 130.2, 131.7, 134.5, 142.1, 147.1, 151.4, 170.9; MS (ESI) *m/z* 486.1 $(M+H)^+$. Anal. Calcd for $C_{17}H_{10}Cl_2IN_3O_2$: C, 42.00; H, 2.07; N, 8.64. Found: C, 42.18; H, 2.23; N, 8.56%.

4-Iodo-5,6-di(p-fluoroanilino)pyridine-2,3-dione (**2c**): Yield (84.3%), Yellow powder, m.p. 185.3–187.2 °C. IR (KBr, cm^{-1}): 3438, 3234, 1727, 1662, 1573, 1499; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.95–7.21 (m, 8H, PhH), 8.33 (s, 1H, NH), 8.82 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 79.0, 115.7, 115.9, 117.2, 117.4, 122.1, 122.2, 128.6, 128.7, 132.0, 132.0, 139.5, 139.5, 141.3, 147.1, 151.2, 159.9, 160.5, 161.8, 162.5, 170.9; MS (ESI) *m/z* 454.2 $(M+H)^+$. Anal. Calcd for $C_{17}H_{10}F_2IN_3O_2$: C, 45.06; H, 2.22; N, 9.27. Found: C, 45.19; H, 2.38; N, 9.49%.

4-Iodo-5,6-di(o-methoxyanilino)pyridine-2,3-dione (**2d**): Yield (80.1%), red powder, m.p. 179.8–181.9 °C. IR (KBr, cm^{-1}): 3444, 3211, 1708, 1654, 1559, 1498; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.85 (s, 6H, CH_3O), 6.92 (d, J = 3 Hz, 2H, PhH), 6.93 (d, J = 2 Hz, 2H, PhH), 6.99 (d, 1H, PhH), 7.00 (d, 1H, PhH), 7.13 (d, 1H, PhH), 7.15 (s, 1H, PhH), 8.41 (s, 1H, NH), 8.94 (s, 1H, PhH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.7, 55.8, 78.1, 111.1, 112.2, 120.0, 121.7, 122.7, 124.7, 127.4, 127.8, 128.3, 132.1, 140.8, 147.2, 148.8, 151.7, 154.2, 171.0; MS (ESI) *m/z* 478.3 $(M+H)^+$. Anal. Calcd for $C_{19}H_{16}IN_3O_4$: C, 47.82; H, 3.38; N, 8.80. Found: C, 48.01; H, 3.56; N, 8.91%.

4-Iodo-5,6-di(m-methylanilino)pyridine-2,3-dione (**2e**): Yield (90.3%), red powder, m.p. 181.6–182.2 °C. IR (KBr, cm^{-1}): 3445, 3239, 1721, 1670, 1566, 1498; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.39 (s, 6H, $2CH_3$), 6.76 (d, J = 11.5 Hz, 2H, PhH), 7.00 (d, J = 6.5 Hz, 2H, PhH), 7.08 (d, J = 8.0 Hz, 1H, PhH), 7.13 (d, J = 8.0 Hz, 1H, PhH), 7.32 (t, J = 5.5 Hz, 1H, PhH), 7.35 (t, J = 7.5 Hz, 1H, PhH), 8.32 (s, 1H, NH), 8.91 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.3, 21.4, 79.1, 117.2, 120.7, 123.4, 126.9, 127.0, 127.7, 128.5, 130.0, 135.7, 138.7, 140.4, 141.0, 143.6, 147.1, 151.5, 171.1; MS (ESI) *m/z* 446.3 $(M+H)^+$. Anal. Calcd for $C_{19}H_{16}IN_3O_2$: C, 51.25; H, 3.62; N, 9.44. Found: C, 51.53; H, 3.80; N, 9.21%.

4-Iodo-5,6-di(o-methylanilino)pyridine-2,3-dione (**2f**): Yield (81.9%), orange powder, m.p. 113.5–116.9 °C. IR (KBr, cm^{-1}): 3436, 3207.23, 1728, 1659, 1559,1505; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.17 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 6.83 (d, 1H, PhH), 7.19–7.21 (m, 2H, PhH), 7.25–7.33 (m, 5H, PhH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.2, 21.3, 78.6, 117.3, 120.9, 123.4, 126.6, 127.1, 127.9, 128.2, 130.1, 136.2, 138.8, 140.7, 141.1, 143.9, 147.0, 151.5, 171.0; MS (ESI) *m/z* 446.3 $(M+H)^+$. Anal. Calcd for $C_{19}H_{16}IN_3O_2$: C, 51.25; H, 3.62; N, 9.44. Found: C, 51.56; H, 3.50; N, 9.63%.

4-Iodo-5,6-di(m-chloroanilino)pyridine-2,3-dione (**2g**): Yield (83.5%), red powder, m.p. 107.0–110.3 °C. IR (KBr, cm^{-1}): 3422, 3217, 1718, 1656, 1587, 1552; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.86 (d, J = 7.5 Hz, 1H, PhH), 6.99 (s, 1H. PhH), 7.09 (d, J = 8.0 Hz, 1H, PhH), 7.20 (s, 1H, PhH), 7.25 (d, J = 3.5 Hz, 1H, PhH), 7.29 (d, J = 8 Hz, 1H, PhH), 7.36 (t, J = 8 Hz, 1H, PhH), 7.41 (t, J = 8 Hz, 1H, PhH), 8.76 (m,1H,NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 81.1, 118.6, 120.7, 124.3, 126.3, 126.3, 127.0, 129.7, 131.3, 134.4, 135.8, 137.1, 141.5, 144.5, 146.9, 151.2, 171.0; MS (ESI) *m/z* 486.1 $(M+H)^+$. Anal. Calcd for $C_{17}H_{10}Cl_2IN_3O_2$: C, 42.00; H, 2.07; N, 8.64. Found: C, 42.28; H, 2.18; N, 8.75%.

4-Iodo-5,6-di(m-methoxyanilino)pyridine-2,3-dione (**2h**): Yield (91.5%), orange powder, m.p. 156.8-158.9 °C. IR (KBr, cm^{-1}): 3444, 3237, 1717, 1655, 1594, 1557; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.838 (s, 6H, $2CH_3$), 6.514 (t, J = 7.5 Hz, 2H, PhH), 6.731 (s, 1H, PhH), 6.807 (t, J = 7.5 Hz, 2H, PhH), 6.863 (d, J = 8 Hz, 1H, PhH), 7.313 (t, J = 8 Hz, 1H, PhH), 7.371 (t, J = 8.5 Hz, 1H, PhH), 8.34 (s, 1H, NH), 8.85 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.4, 55.5, 79.7, 106.3, 111.9, 112.1, 112.2, 112.9, 118.8, 129.4, 131.2, 136.9, 141.2, 144.9,147.1, 151.3, 159.9, 161.1, 171.1; MS (ESI) *m/z* 478.3 $(M+H)^+$. Anal. Calcd for $C_{19}H_{16}IN_3O_4$: C, 47.82; H, 3.38; N, 8.80. Found: C, 47.98; H, 3.56; N, 8.95%.

4-Iodo-5,6-di(p-methoxyanilino)pyridine-2,3-dione (**2i**): Yield (85.5%), yellow powder, m.p. 113.7–114.9 °C. IR (KBr, cm^{-1}): 3426, 3235, 1714, 1657, 1567, 1506; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 3.86 (s, 3H), 6.93–7.27 (m, 8H, PhH), 8.40 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.4, 55.5, 77.5, 113.8, 115.5, 122.0, 128.4, 128.7, 136.3, 140.5, 147.2, 151.6, 158.0, 158.5, 173.2; MS (ESI) *m/z* 478.3 $(M+H)^+$. Anal. Calcd for $C_{19}H_{16}IN_3O_4$: C, 47.82; H, 3.38; N, 8.80. Found: C, 48.01; H, 3.55; N, 8.62%.

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