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Dyes and Pigments 62 (2004) 101–105

DYES and PIGMENTS
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A facile synthesis of 6,6′- and 5,5′-dihalogenoindigos

Yasuhiro Tanoue[a,*], Kazunori Sakata[b], Mamoru Hashimoto[b],
Moritsugu Hamada[a], Norihisa Kai[a], Takeshi Nagai[a]

[a]Department of Food Science and Technology, National Fisheries University, Shimonoseki, Yamaguchi 759-6595, Japan
[b]Department of Applied Chemistry, Faculty of Engineering, Kyushu Institute of Technology, Tobata-ku, Kitakyushu 804-8550, Japan

Received 2 June 2003; received in revised form 19 June 2003; accepted 14 July 2003

Abstract

Our convenient synthetic method for Tyrian purple was applied to syntheses of 6,6′- and 5,5′- dihalogenoindigos. The dihalogenoindigos were easily obtained by three steps of reactions from the commercially available haloindoles. Iodination of the haloindoles, followed by acetoxylation with silver acetate in acetic acid, afforded 5- or 6-halo-3-acetoxyindoles, whose alkaline hydrolysis accompanying air oxidation gave the corresponding dihalogenoindigos. The first ^{1}H NMR spectrum of 6,6′-difluoroindigo was taken in dimethyl sulfoxide.

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Keywords: Tyrian purple; Royal purple; 6,6′-Dibromoindigo; Dihalogenoindigo; 3-Iodo-halogenoindole; 3-Acetoxy-6-fluoroindole

1. Introduction

Tyrian purple, royal purple and ancient purple are all synonyms for a dye of molluscan origin and were used as valuable purple dyes of garments for ancient exalted personages such as princes and nobles in the districts along the Mediterranean [1,2]. Precursors of Tyrian purple are contained in the hypobranchial glands of various species of gastropods of the families Muricidae and Thaidinae, and converted into Tyrian purple by the action of sunlight and purpurase [3,4]. In 1909, Friedländer isolated 1.4 g of the dye from 12 000 specimens of the gastropod *Murex brandaris* and identified it as 6,6′-dibromoindigo **4a** [5].

A number of attempts to synthesize Tyrian purple **4a** have already been made. Successful syntheses of **4a** reported thus far required many steps because of the use of di- or tri-substituted benzenes as the starting materials [6–8], with only one exception [9]. We have already reported a convenient synthesis of **4a** from the commercially available 6-bromoindole **1a** [10]. The present paper describes applications of this method to syntheses of 6,6′- and 5,5′-dihalogenoindigos and the first ^{1}H NMR spectrum of 6,6′-difluoroindigo (**4e**).

2. Results and discussion

A schematic overview of syntheses of 6,6′- and 5,5′- dihalogenoindigos was shown in Scheme 1. Treatment of the commercially available 6- or 5-halogenoindoles **1b**–**f** with iodine (1 equivalent),

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* Corresponding author. Tel.: +81-832-86-5111; fax: +81-832-86-7434.

E-mail address: tanoue@fish-u.ac.jp (Y. Tanoue).

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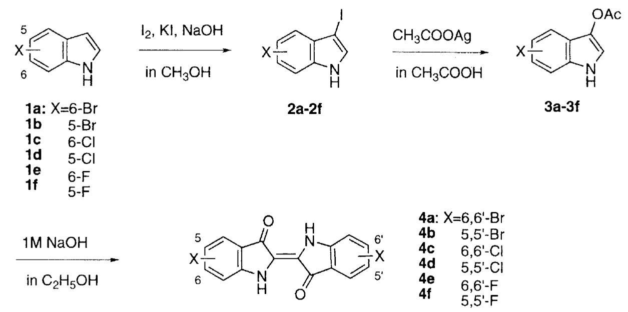
doi:10.1016/S0143-7208(03)00150-5



Scheme 1.

potassium iodide (1 equivalent), and sodium hydroxide (1 equivalent) in methanol overnight at room temperature gave 3-iodo-6- or 5-halogenoindoles **2b–f**, which were used for the following reaction without purification because of their lability [11]. The indoles **2b–f** were treated with silver acetate [12] (1.5 equivalent) in acetic acid at 90 °C for 1 h. As expected, the reaction proceeded regioselectively at the 3-position of **2b–f** to produce the desired 3-acetoxy- 6- or 5-haloindoles **3b–f**.

The structure determination of **3e** was described as a typical example. The ^{13} C NMR spectrum showed signals at δ130.5 (singlet) and 160.3 (doublet, $J_{6\text{-F}} = 238$ Hz) due to C-3 and C-6, respectively. The mass spectrum of the product clearly exhibited a molecular ion peak at m/z 193. These data as well as an elemental analysis indicated the structure of **3e**.

Hydrolysis of **3b–f** was carried out in aqueous ethanol containing sodium hydroxide at room temperature for 2 h to give 6,6′- or 5,5′-dihalogenoindigos **4b–f**.

Although there have been a report [13] for UV-visible spectra of the dihalogenoindigos in tetrachloroethane, their NMR spectra have, to our knowledge, not yet been reported, because they are poorly soluble in common organic solvents. Fortunately, we were able to take the ^{1}H NMR spectrum of 6,6′-difluoroindigo **4e**, since it only was slightly soluble in dimethyl sulfoxide. The spectrum was shown in Fig. 1.

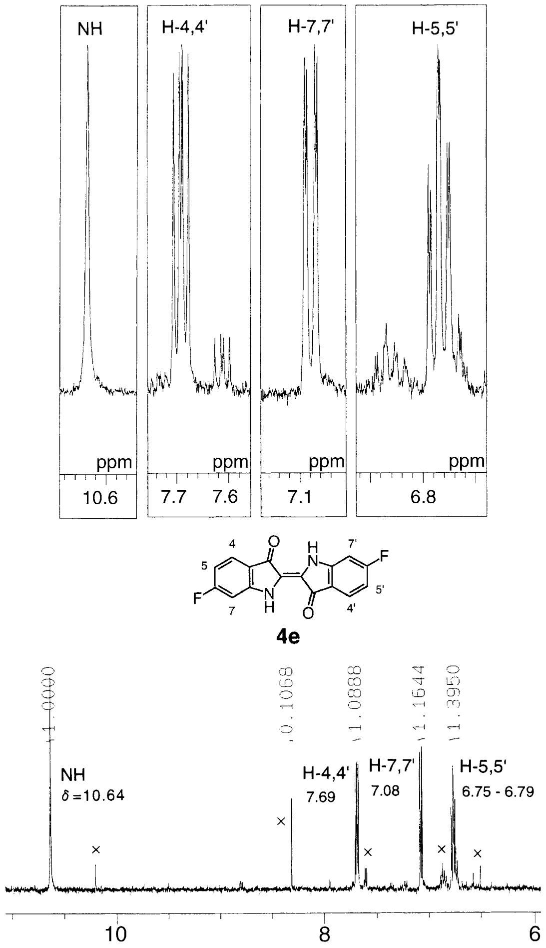


Fig. 1. The spectrum of 6,6′-difluoroindigo (**4e**) in dimethyl sulfoxide.

In the infrared spectra of dihalogenoindigos **4a–f**, N–H, C = O and C = C stretching vibrations

Table 1
Stretching vibrations in infrared spectra of dihalogenoindigos

Compound	N–H	C = O	C = C (cm^{-1})
6,6′-Dibromoindigo **4a**	3380	1634	1608
6,6′-Dichloroindigo **4c**	3385	1632	1618
6,6′-Difluoroindigo **4e**	3390	1631	1594
5,5′-Dibromoindigo **4b**	3285	1628	1607
5,5′-Dichloroindigo **4d**	3280	1627	1609
5,5′-Difluoroindigo **4f**	3270	1624	1593
Indigo	3270	1626	1613

were summarized in Table 1. The absorption of N-H the stretching vibrations in 6,6′-substituted compounds occurs at about 100 cm^{-1} higher wave number than that in 5,5′-substituted compounds.

3. Experimental

3.1. General

^{1}H NMR and ^{13}C NMR spectra were taken on a JEOL JNM-EX90A (90 MHz) and JEOL JNM-A500 (500 MHz) spectrometers in $CDCl_3$ and $(CD_3)_2SO_2$ solutions. EI mass spectra were performed with a JEOL JMS-SX 102A mass spectrometer at 70 eV ionization energy. Infrared spectra were recorded on a Shimadzu IR 470 and HORIBA FT-730 spectrometers. Melting points were observed with a Yanaco MS-S3 micro melting point apparatus (hot-plate type). Elemental analyses were determined with a Yanaco CHN Corder MT-3. For preparative column chromatography, Wakogel C-200 silica gel was employed. Haloindoles (**1b–f**) were purchased from Tokyo Kasei Kogyo Co. Ltd (Tokyo, Japan).

3.2. Preparation of 3-acetoxy-6- or 5-haloindoles (3b–f)

Synthesis of 3-acetoxy-6-fluoroindole (**3e**) was described as a typical example. To a solution of 6-fluoroindole (**1e**) (100 mg, 0.74 mmol) and sodium hydroxide (29.6 mg, 0.74 mmol) in metanol (10 ml) were added iodine (188 mg, 0.74 mmol) and an aqueous solution (1 ml) of potassium iodide (123 mg, 0.74 mmol). After the mixture was stirred at room temperature for 3 h, water (20 ml) was added. The resulting precipitate was collected by filtration, washed with water, and dried under reduced pressure to obtain 6-fluoro-3-iodoindole (**2e**) (153 mg, 0.584 mmol), which was used for the following reaction without purification because of its lability. Silver acetate (146 mg, 0.876 mmol) was added to a solution of **2e** in acetic acid (10 ml). After stirring for 1 h at 90 °C, the mixture was cooled to room temperature and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$ to give 3-acetoxy-6-fluoroindole (**3e**) (73 mg, 51% yield).

3.2.1. 3-Acetoxy-5-bromoindole (3b)

(41% yield): colorless plate crystals (hexane: ethyl acetate = 20:1); mp 131–132 °C; IR (KBr) 3330 (NH), 1741 (C = O), 1459, 1370, 1286, 1221, 1083, 797 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ2.35 (*s*, 3H, CH_3), 7.13 (*dd*, $J_{6\text{-}7} = 8.9$, $J_{6\text{-}4} = 1.7$ Hz, 1H, H-6), 7.25-7.27 (*m*, 2H, H-2, H-7), 7.67 (*d*, $J_{4\text{-}6} = 1.7$ Hz, 1H, H-4), 7.97 (broad, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.89 (CH_3), 112.90 (C-7), 113.09 (C-5), 114.65 (C-2), 120.02 (C-4), 121.51 (C-9), 125.68 (C-6), 129.65 (C-3), 131.64 (C-8), 168.76 (C = O); MS *m*/*z* (rel. intensity, %) 255 (M + 2, 38.3%), 253 (M^+, 39.1), 216 (49), 213 (100), 211 (99.7), 187 (19), 132 (27). Anal. calcd for $C_{10}H_8BrNO_2$: C, 47.27; H, 3.17; N, 5.51. Found: C, 47.25; H, 3.22; N, 5.53.

3.2.2. 3-Acetoxy-6-chloroindole (3c)

(51% yield): colorless needles (hexane); mp 109–110 °C; IR (KBr) 3390 (NH), 1742 (C = O), 1619, 1333, 1223, 1076, 907, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.36 (*s*, 3H, CH_3), 7.09 (*dd*, $J_{5\text{-}4} = 8.5$, $J_{5\text{-}7} = 1.8$ Hz, 1H, H-5), 7.25 (*d*, $J_{7\text{-}5} = 1.8$ Hz, 1H, H-7), 7.26 (*s*, 1H, H-2), 7.44 (*d*, $J_{4\text{-}5} = 8.5$ Hz, 1H, H-4), 7.92 (broad, 1H, NH); ^{13}C NMR (CDCl$_3$) δ 20.93 (CH$_3$), 111.28 (C-7), 113.97 (C-2), 118.38 (C-4), 118.57 (C-9), 120.71 (C-5), 128.75 (C-6), 130.41 (C-3), 133.30 (C-8), 168.76 (C=O); MS *m/z* (rel. intensity, %) 211 (M + 2, 20%), 209 (M$^+$, 55), 169 (77), 167 (100), 138 (46). Anal. calcd for $C_{10}H_8ClNO_2$: C, 57.30; H, 3.85; N, 6.68. Found: C, 57.28, H, 4.00; N, 6.62.

3.2.3. *3-Acetoxy-5-chloroindole (**3d**)*

(39% yield): colorless plate crystals (hexane: ethyl acetate = 20:1); mp 124–126 °C; IR (KBr) 3340 (NH), 1744 (C=O), 1287, 1221, 1091, 802 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.36 (*s*, 3H, CH$_3$), 7.13 (*dd*, $J_{6\text{-}7} = 8.5$, $J_{6\text{-}4} = 2.0$ Hz, 1H, H-6), 7.17 (*d*, $J_{7\text{-}6} = 8.5$ Hz, 1H, H-7), 7.27 (*s*, 1H, H-2), 7.51 (*d*, $J_{4\text{-}6} = 2$ Hz, 1H, H-4), 7.97 (broad, 1H, NH); ^{13}C NMR (CDCl$_3$) δ 20.89 (CH$_3$), 112.51 (C-8), 114.84 (C-2), 116.93 (C-4), 120.88 (C-9), 123.15(C-6), 125.65 (C-5), 129.82 (C-3), 131.39 (C-8), 168.81 (C=O); MS *m/z* (rel. intensity, %), 211 (M + 2, 32%), 209 (M$^+$, 73), 169 (88), 168 (67), 167 (100), 166 (76), 138 (58), 132 (39), 111 (53). Anal. calcd for $C_{10}H_8ClNO_2$: C, 57.30; H, 3.85; N, 6.68. Found: C, 57.08; H, 3.85; N, 6.66.

3.2.4. *3-Acetoxy-6-fluoroindole (**3e**)*

(51% yield): colorless plate crystals (hexane); mp 139–140 °C; IR (KBr) 3380 (NH), 1743 (C=O), 1629, 1598, 1338, 1227, 1122, 806 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.36 (*s*, 3H, CH$_3$), 6.88–6.92 (*m*, 1H, H-5), 6.96 (*dd*, $J_{7\text{-F}} = 9.6$, $J_{7\text{-}5} = 1.8$ Hz, 1H, H-7), 7.25 (*d*, $J_{2\text{-}1} = 2.8$ Hz, 1H, H-2), 7.45 (*dd*, $J_{4\text{-}5} = 8.5$, $J_{4\text{-F}} = 5.2$ Hz, 1H, H-4), 7.91 (broad, 1H, NH); ^{13}C NMR (CDCl$_3$) δ 20.93 (CH$_3$), 97.62 (*d*, $J_{7\text{-F}} = 26.9$ Hz, C-7), 108.92 (*d*, $J_{5\text{-F}} = 24.8$ Hz, C-5), 113.52 (C-2), 116.67 (C-9), 118.37 (*d*, $J_{4\text{-F}} = 9.2$ Hz, C-4), 130.47 (C-3), 133.00 (*d*, $J_{8\text{-F}} = 12.4$ Hz, C-8), 160.32 (*d*, $J_{6\text{-F}} = 238$ Hz, C-6), 168.77 (C=O); MS *m/z* (rel. intensity, %) 193 (M$^+$, 58%), 152 (55), 151 (100), 150 (59), 123 (57), 122 (59), 96 (39), 95 (58), 94 (55), 75 (52). Anal. calcd for $C_{10}H_8FNO_2$: C, 62.18; H, 4.17; N, 7.25. Found: C, 62.19; H, 4.20; N, 7.20.

3.2.5. *3-Acetoxy-5-fluoroindole (**3f**)*

(32% yield): colorless prisms (hexane:ethyl acetate = 20:1), mp 138–140 °C; IR (KBr) 3340 (NH), 1747 (C=O), 1490, 1296, 1222, 1187, 1053, 935, 852, 797 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.35 (*s*, 3H, CH$_3$), 6.91–6.96 (*m*, 1H, H-6), 7.16–7.20 (*m*, 2H, H-4, H-7), 7.29 (*d*, $J_{2\text{-}1} = 2.8$ Hz, 1H, H-2), 7.94 (broad, 1H, NH): ^{13}C NMR (CDCl$_3$) δ 20.89 (CH$_3$), 102.39 (*d*, $J_{4\text{-F}} = 24.8$ Hz, C-4), 111.39 (*d*, $J_{6\text{-F}} =$ 26.9 Hz, C-6), 112.29 (*d*, $J_{7\text{-F}} = 9.3$ Hz, C-7), 115.27 (C-2), 120.10 (*d*, $J_{9\text{-F}} = 10.3$ Hz, C-9), 129.63 (C-3), 130.45 (*d*, $J_{8\text{-F}} = 4.1$ Hz, C-8), 157.80 (*d*, $J_{5\text{-F}} = 235$ Hz, C-5), 168.82 (C=O); MS *m/z* (rel. intensity, %) 193 (100%), 152 (86), 151 (96), 150 (97), 123 (88), 122 (94), 96 (65), 95 (89), 94 (69), 75 (63). Anal. calcd for $C_{10}H_8FNO_2$: C, 62.18, H, 4.17; N, 7.25. Found: C, 61.53; H, 4.21; N, 7.15.

3.3. *Preparation of 6,6′- or 5,5′-dihalogenoindigos (**4b–f**)*

Synthesis of 6,6′-difluoroindigo (**4e**) was described as a typical example. To a solution of **3e** (51 mg, 0.262 mmol) in ethanol (5 ml) was added aqueous 1M sodium hydroxide (10 ml). After the mixture was stirred at room temperature for 2 h, water was added. The resulting precipitate was collected by filtration, washed with water, and dried to give **4e** (29 mg, 73% yield).

3.3.1. *5,5′-Dibromoindigo (**4b**)*

(70% yield): dark blue solid; mp > 300 °C; IR (KBr) 3285 (NH), 1628, 1607, 1458, 1187, 1119, 618 cm^{-1}; MS *m/z* (rel. intensity, %) 422 (M + 4, 100), 420 (M + 2, 100), 418 (M$^+$, 50), 392 (7), 313 (7), 311 (7), 285 (12), 283 (12), 182 (18). Anal. calcd for $C_{16}H_8Br_2N_2O_2$: C, 45.75; H, 1.92; N, 6.67. Found: C, 45.61; H, 2.21; N, 6.41.

3.3.2. *6,6′-Dichloroindigo (**4c**)*

(73% yield): purplish red solid; mp > 300 °C; IR (KBr) 3385 (NH), 1632, 1618, 1578, 1441, 1316, 1159, 1082, 1059, 912 cm^{-1}; MS *m/z* (rel. intensity, %) 334 (M + 4, 11%), 332 (M + 2, 65), 330 (M$^+$, 100), 302 (12), 239 (17), 138 (24). Anal. calcd for $C_{16}H_8Cl_2N_2O_2$: C, 58.03; H, 2.43; N, 8.46. Found: C, 57.40; H, 2.64; N, 8.21.

3.3.3. *5,5′-Dichloroindigo (**4d**)*

(68% yield): dark blue solid; mp > 300 °C; IR (KBr) 3280 (NH), 1627, 1609, 1461, 1187, 1141, 1120, 642 cm^{-1}; MS *m/z* (rel. intensity, %) 334 (M + 4, 11%), 332 (M + 2, 65), 330 (M$^+$, 100), 302 (10), 267 (11), 239 (18), 192 (10), 138 (21). Anal. calcd for $C_{16}H_8Cl_2N_2O_2$: C, 58.03; H, 2.43; N, 8.46. Found: C, 57.55; H, 2.71; N, 8.25.

3.3.4. 6,6′-Difluoroindigo (4e)

(73% yield): purplish red solid; mp > 300 °C; IR (KBr) 3390 (NH), 1631, 1594, 1451, 1328, 1296, 1181, 1126, 1099, 847 cm^{-1}; ^{1}H NMR (DMSO) δ6.75–6.79 (*m*, 2H, H-5,5′), 7.08 (*dd*, $J_{7\text{-F}} = J_{7'\text{-F}} = 10.1$, $J_{7\text{-}5} = J_{7'\text{-}5'} = 2.1$ Hz, 2H, H-7,7′), 7.69 (*dd*, $J_{4\text{-}5} = J_{4'\text{-}5'} = 8.5$, $J_{4\text{-F}} = J_{4'\text{-F}} = 5.8$ Hz, 2H, H-4,4′), 10.64 (*s*, 2H, 2NH); MS *m/z* (rel. intensity, %) 298 (M$^+$, 100%), 270 (24), 241 (22), 176 (10), 175 (8.8), 149 (9.6), 122 (61), 121 (17), 94 (38). Anal. calcd for $C_{16}H_8F_2N_2O_2$: C, 64.43; H, 2.70; N, 9.39. Found: C, 63.97; H, 2.92; N, 9.15.

3.3.5. 5,5′-Difluoroindigo (4f)

(70% yield): dark blue solid; mp > 300 °C; IR (KBr) 3270 (NH), 1624, 1593, 1478, 1459, 1386, 1314, 1261, 1179, 1133, 1105, 1053, 820, 685 cm^{-1}; MS *m/z* (rel. intensity, %), 298 (M$^+$, 100%), 270 (21), 241 (24), 176 (12), 175 (8), 149 (8), 122 (27), 121 (20), 94 (17). Anal. calcd for $C_{16}H_8F_2N_2O_2$: C, 64.43; H, 2.70; N, 9.39. Found: C, 64.39; H, 3.09; N, 9.03.

4. Conclusions

We found that our convenient synthetic method for Tyrian purple was applicable to syntheses of 6,6′- and 5,5′-dihalogenoindigos. The advantages of the method are short steps using commercially available starting materials and easy work-up procedures. The first ^{1}H NMR spectrum of 6,6′-difluoroindigo was taken in dimethyl sulfoxide.

Acknowledgements

We are grateful to Misses M. Nouno and H. Yamada, and Messrs Y. Sasaki and J. Yamamoto for their technical assistance. We are also thankful to the Center for Instrumental Analysis, Kyushu Institute of Technology for elemental analyses, mass spectra and NMR (500 MHz) spectra.

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