

Novel electrophilic aromatic iodine substitution of some naphtholic Schiff bases

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Abstract

During the ring closure trial of the naphtholic Schiff bases (**1a-d**) we found that iodine was incorporated into the phenyl ring. The structures of the products (**2a-e**) obtained with this novel substitution reaction, were determined by NMR (¹H-NMR, ¹³C-NMR, 2D-NMR), mass, IR and UV spectra as well as chemical analysis.

Keywords: Aromatic iodination, electrophilic aromatic substitution, iodoarenes, Schiff base

Introduction

Iodoaromatic compounds are valuable and versatile synthetic intermediates in many domains of synthetic organic chemistry, medicine and biochemistry.^{1,2} Direct iodination of aromatic compounds is difficult due to the poor electrophilic strength of molecular iodine compared to that of molecular chlorine and bromine. Iodination of aromatic compounds was carried out by using molecular iodine together with Lewis acid or a strong oxidizing agent such as Ag₂SO₄, NaIO₄, HIO₄, NaOCl, liquid SO₃, iodic acid,³ nitric acid and sulfuric acid,⁴ sulfur trioxide and hydrogen peroxide.⁵⁻⁹ Recently, direct iodination methods have been reported using various iodonium donating reagents, such as iodine/Na₂S₂O₈,¹⁰ iodine-(NH₄)₂S₂O₈-CuCl₂-Ag₂SO₄,¹¹ NaOCl-NaI,¹² bis(pyridineiodonium(I))tetrafluoroborate-CF₃SO₃H,¹³ iodine silver sulfate,¹⁴ NIS-CF₃SO₃H,² iodine-mercury salts,¹⁵ iodine monochloride,¹⁶ mercury(II)-oxide-iodine,¹⁷ bis(sym-collidine)iodine(I)hexafluorophosphate,¹⁸ iodine-di-iodine pentoxide,¹⁹ NIS (*N*-iodosuccinimide),²⁰ iodine-nitrogen dioxide,²¹ iodine-F-TEDA-BF₄,²² iodine-iodic acid,²³ *n*-BuLi-CF₃CH₂I,²⁴ NH₄I-oxone,²⁵ ICl.²⁶

However, most of these methods require a high reaction temperature and long reaction times,²⁰ work in low yields,²⁷ involve toxic heavy metals, involve harsh conditions, and generate costly or complex and hazardous waste.^{25,28-30} Therefore, attempts have been made to overcome

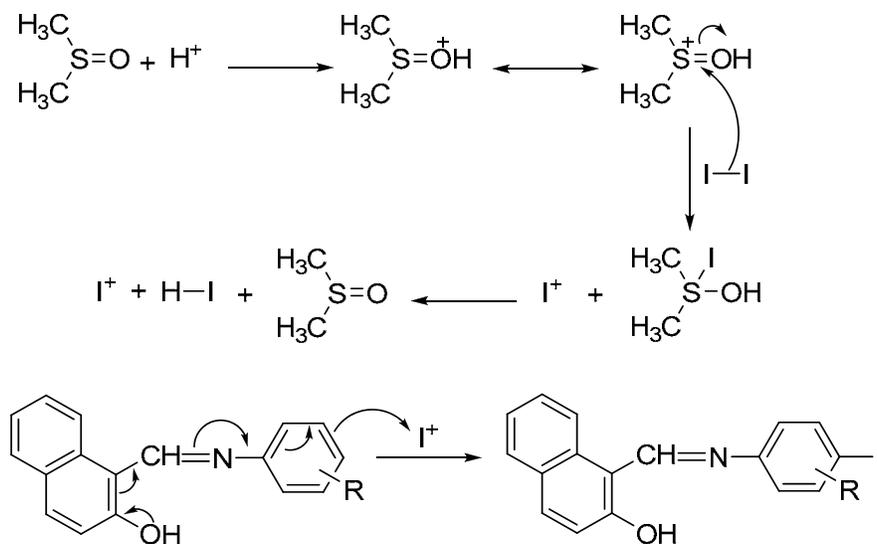
^{13}C -NMR spectrum (CDCl_3) of the product showed a peak at 90.8 ppm which can be attributed to the iodine substituted carbon. So instead of the ring closure, iodine was substituted into the phenyl ring of the Schiff base (**2a**). In the ^1H -NMR spectrum (CDCl_3) of the product one-proton singlet at 15.25 ppm was attributed to the naphtholic -OH and two doublets at 7.11 and 7.76 ppm revealed that the iodine was substituted in para-position to the azomethine group (-CH=N-) in the phenyl ring. From the HETCOR (CDCl_3) of the compound we assigned the signal to the azomethine group at 9.33 (155.6), and the signals 8.09 (136.7), 7.82 (129.4), 7.76 (138.7), 7.73 (121.6), 7.11 (122.4), 7.11 (118.9) were assigned to the H-4 (C-4), H-5 (C-5), H-3' and H-5' (C-3' and C-5'), H-8 (C-8), H-2' (C-2') and H-3 (C-3) carbons and protons respectively. The other two signals at 7.53 (128.2) and 7.35 (123.7) were due to the H-7 (C-7) and H-6 (C-6) protons and carbons of the product. These spectroscopic data and the chemical analysis were in accordance with 1-[(4-iodophenyl)imino]methyl}-2-naphthol (**2a**).

Since we obtained the iodine substituted Schiff base **2a** instead of ring closed product **3a** we tried iodine substitution of Schiff base **1b**, bearing an *o*-methyl group, with $\text{DMSO-I}_2\text{-H}^+$ under the same reaction conditions. The crude mixture showed the presence of one new compound together with the unreacted Schiff base **1b**. It was purified with preparative TLC ($\text{SiO}_2/\text{toluene}$) ($R_f=0.26$) and crystallized from alcohol (yellow crystals, mp: 136-138 °C). Mass spectrum of the purified compound **2b** gave a molecular ion peak at 387.0 confirming iodine substitution. Chemical analysis of the compound was in agreement with the iodine substituted structure. In the IR spectrum there were -OH and -CH=N- peaks at 3500 and 1625 cm^{-1} . In ^{13}C -NMR spectrum of **2b** there were C-I and -CH=N- peaks at 90.9 and 154.8 ppm respectively and together with the other peaks they confirmed the Schiff base structure **2b**. From the ^1H -NMR spectrum of the product it was clear that the substitution occurred to the para-position of the phenyl ring with respect to the azomethine group.

Since in the *o*-methyl substituted Schiff base (**1b**) iodine was substituted to the para-position of the phenyl ring (**2b**), we investigated the effect of a *m*-methyl group in the reaction. When applying the same reaction conditions, two compounds (**2c** and **2d**) were isolated by preparative TLC ($\text{SiO}_2/\text{toluene}$). The compound with $R_f=0.25$ was crystallized from alcohol delivering yellow crystals (mp: 96 °C). ^1H -NMR and ^{13}C -NMR spectra showed that iodine again was substituted in para-position of the phenyl ring with respect to the azomethine group (**2c**). For the compound with $R_f=0.46$ (yellow crystals, mp: 146-148 °C) mass spectra and the chemical analysis confirmed the iodine substituted Schiff base (**2d**) with iodine substituted in the ortho-position with respect to the azomethine group and para-position relative to the - CH_3 group. ^1H -NMR and ^{13}C -NMR spectra as well as the mass spectrum and chemical analysis were in agreement with this structure.

Subsequently, with a blocked para-position we wished to explore the effect on the substitution reaction. After heating of the Schiff base **1e** with $\text{DMSO-I}_2\text{-H}^+$ under the same reaction condition we obtained one product (**2e**) (mp: 142 °C) together with the unreacted Schiff base (**1e**). Mass spectrum of the isolated product was again 387.0 and chemical analysis confirmed the expected elemental composition of **2e**. Analysis of ^1H -NMR and ^{13}C -NMR spectra

showed that iodine was substituted in the ortho-position with respect to the azomethine group and meta-position relative to the $-CH_3$ group in the phenyl ring. For the mechanism of the iodine substitution reaction we suggest the mechanism in Scheme 2.



Scheme 2. Electrophilic aromatic iodine substitution mechanism.

Experimental Section

General Procedures. All melting points were taken in open capillaries and uncorrected. The IR spectra in KBr were recorded on Mattson 1000 FTR spectrometer and JASCO ST / IR-420 machine and UV spectra on Unicam UV2-100/Visible spectrometer and 150-20 Hitachi spectrometer. 1H and ^{13}C -NMR spectra were determined at Bruker AC 200L and Bruker 400 MHz spectrometer using $CDCl_3$. Mass spectra were obtained in a (LS/MS-APCI) Agilent 1100 MSD Instrument. Elemental analyses were obtained LECO CHNS 932 Machine. Merck Kieselgel HF₂₅₄ type-60 and Kieselgel 40-60 μm type were used for TLC. For analytical work 0.25 mm, for preparative work 0.75 mm plates were used. All solvents and reagents used were analytical reagent grade.

The synthesis of the Schiff bases (1a-d)

Schiff bases (**1a-d**) were synthesized according to the method of Sawich and coworkers.³¹ Their structures were determined by IR, UV and ^{13}C -NMR spectra.

Reaction of Schiff bases (1a-d) with $DMSO-H^+I_2$

Schiff bases (**1a-d**) (4 mmol) were dissolved in DMSO (16 ml) and the H_2SO_4 was added until the pH was approximately 5.0 and then catalytic amount I_2 for (**1a**), for the others (**1b-d**)

equivalent amount (4 mmol) I_2 was added to this solution. The reaction mixture was heated at 125-130 °C for 12 hours under N_2 atmosphere. The crude product was washed with iced water to remove DMSO and dissolved with 10% $Na_2S_2O_3$ to remove the excess iodine. Then the crude product was extracted with CH_2Cl_2 (30 ml). After evaporation of the solvent *in vacuo* crude product was purified by preparative TLC (SiO_2 /toluene) and crystallized from ethanol.

1-{(4-iodophenyl)imino)methyl}-2-naphthol (2a). Yield: 17.6%. mp: 142-144 °C. Mass spectrum: m/z = [373.0, 100%], 245.0 [M-HI, 41.6%]⁺, 227.0 [M-(HI+H₂O), 31.6%]⁺. Anal: Calcd for $C_{17}H_{12}INO$ (373.19): C, 54.71; H, 3.24; N, 3.75. Found: C, 54.16; H, 4.35; N, 3.23. IR (KBr) ν_{max} : 3500, 1625, 1574-1497 cm^{-1} . UV (EtOH) $\lambda_{max}(\log \epsilon)$: 284.4 (0.412), 317.2 (0.585), 357.2 (0.414), 461.6 nm (0.070). ¹H-NMR (400 MHz, $CDCl_3$): δ 7.11 (2H, d, $J=8.5$ Hz, H-3 and H-2'), 7.35 (1H, dt, $J=1.02, 7.7$ Hz, H-6), 7.53 (1H, dt, $J=1.02, 7.4$ Hz, H-7), 7.73 (1H, d, $J=9.0$ Hz, H-8), 7.76 (2H, d, $J=8.5$ Hz, H-3'), 7.81 (1H, d, $J=9.0$ Hz, H-5), 8.09 (1H, d, $J=8.5$ Hz, H-4), 9.33 (1H, d, $J=1.82$ Hz, (-CH=N-), 15.25 (1H, brd.s, naphtholic -OH). ¹³C-NMR (400 MHz, $CDCl_3$): δ 90.8 (C-4'), 109.0 (C-1), 118.9 (C-3), 121.6 (C-8), 122.4 (C-2'), 123.7 (C-6), 127.5 (C-4a), 128.2 (C-7), 129.4 (C-5), 133.0 (C-8a), 136.7 (C-4), 138.7 (C-3'), 145.8 (C-1'), 155.6 (-CH=N-), 168.9 (C-2). HETCOR ($CDCl_3$): 9.33, -CH=N- (155.6, -CH=N- azomethine carbon), 8.09, H-4 (136.7, C-4), 7.81, H-5 (129.4, C-5), 7.76, H-3' (138.7, C-3'), 7.73, H-8 (121.6, C-8), 7.53, H-7 (128.2, C-7), 7.35, H-6 (123.7, C-6), 7.11, H-2' (122.4, C-2'), 7.11, H-3 (118.9, C-3).

1-{(4-iodo-2-methylphenyl)imino)methyl}-2-naphthol (2b). Yield: 39.4%. mp: 136-138 °C. Mass spectrum: m/z = M^+ [387.0], [259.0 (M-HI, 23.6%)]⁺, [244.0 (M-C₁₀H₈O, 16.3%)]⁺. Anal: Calcd for $C_{18}H_{14}INO$ (387.21): C, 55.83; H, 3.64; N, 3.62. Found: C, 56.40; H, 4.55; N, 3.34. IR (KBr) ν_{max} : 3500, 1625, 1600-1497 cm^{-1} . UV (EtOH) $\lambda_{max}(\log \epsilon)$: 288.0 (0.701), 322 (0.250), 360.0 (0.148), 445.2 (0.139), 466.0 nm (0.135). ¹H-NMR (400 MHz, $CDCl_3$): δ 2.41 (3H, s, -CH₃), 7.02 (1H, d, $J\approx 8.5$, H-6'), 7.09 (1H, d, $J=9.0$ Hz, H-3), 7.34 (1H, dt, $J\approx 7.5$ Hz, H-6), 7.52 (1H, dt, $J=7.5$, H-7), 7.62 (1H, d, $J\approx 7.0$ Hz, H-5'), 7.62 (1H, brd.s, H-3'), 7.82 (1H, d, $J=9.0$ Hz, H-5), 7.72 (1H, d, $J=8.0$ Hz, H-8), 8.10 (1H, d, $J\approx 8.5$ Hz, H-4), 9.30 (1H, d, $J=3.0$ Hz, -CH=N), 15.51 (1H, brd.s, naphtholic -OH). ¹³C NMR (400 MHz, $CDCl_3$): δ 17.8 (-CH₃), 90.9 (C-4'), 109.7 (C-1), 118.8 (C-6'), 118.9 (C-3), 121.8 (C-8), 123.7 (C-6), 127.4 (C-4a), 128.2 (C-7), 129.4 (C-5), 133.0 (C-8a), 133.6 (C-2'), 136.2 (C-4), 136.8 (C-5'), 139.7 (C-3'), 144.4 (C-1'), 154.8 (-CH=N-), 169.5 (C-2).

1-{(4-iodo-3-methylphenyl)imino)methyl}-2-naphthol (2c). Yield: 29.2%. mp: 96 °C. Mass spectra: m/z = M^+ [387.0], [259.0 (M-HI, 100%)]⁺, [244.0 (M-C₁₀H₈O, 22.1%)]⁺. Anal: Calcd for $C_{18}H_{14}INO$ (387.21): C, 55.83; H, 3.64; N, 3.62. Found: C, 56.49; H, 3.76; N, 3.39. IR (KBr) ν_{max} : 3150, 1625, 1574-1497 cm^{-1} . UV (EtOH) $\lambda_{max}(\log \epsilon)$: 286.4 (0.560), 316.8 (0.560), 358.8 (0.396), 443.6 (0.080), 464.0 (0.079) nm. ¹H-NMR (400 MHz, $CDCl_3$): δ 2.45 (3H s, -CH₃), 6.86 (1H, d, $J\approx 7.5$ Hz, H-6'), 7.05 (1H, d, $J\approx 9.0$ Hz, H-3), 7.17 (1H, s, H-2'), 7.31 (1H, t, $J=7.5$ Hz, H-6), 7.49 (1H, t, $J=7.8$ Hz, H-7), 7.68 (1H, d, $J\approx 8.0$ Hz, H-5'), 7.76 (1H, d, $J=7.5$ Hz, H-8), 7.81 (1H, d, $J\approx 9.0$ Hz, H-5), 8.05 (1H, d, $J\approx 8.5$ Hz, H-4), 9.24 (1H, brd.s, -CH=N-), 15.36 (1H, brd.s, naphtholic -OH). ¹³C NMR (400 MHz, $CDCl_3$): δ 22.9 (-CH₃), 97.6 (C-4'), 108.9 (C-1), 118.9 (C-2'), 119.1 (C-3), 121.6 (C-8), 121.9 (C-6'), 123.6 (C-6), 127.3 (C-4a), 128.1 (C-7), 129.4 (C-

5), 133.1 (C-8a), 136.8 (C-4), 139.8 (C-5'), 142.8 (C-3'), 145.5 (C-1'), 154.7 (-CH=N-), 169.8 (C-2).

1-[(2-iodo-5-methylphenyl)imino]methyl-2-naphthol (2d). Yield: 19.4%. mp: 146-148 °C. Mass spectra: $m/z = M^+$ [387.0], [259.0 (M-HI, 39.3%)]⁺, [106.1 (C₈H₁₀, 100%)]⁺. Anal: Calcd for C₁₈H₁₄INO (387.21): C, 55.83; H, 3.64; N, 3.62. Found: C, 56.02; H, 4.17; N, 2.97. IR (KBr) ν_{\max} : 3500, 1625, 1574-1497 cm⁻¹. UV (EtOH) $\lambda_{\max}(\log \epsilon)$: 288.4 (0.738), 316.8 (0.376), 338.8 (0.376), 359.6 (0.419), 462.4 (0.090) nm. ¹H-NMR (400 MHz, CDCl₃): δ 2.39 (3H, s, -CH₃), 6.81 (1H, d, $J=8.0$ Hz, H-4'), 7.04 (1H, s, H-2'), 7.18 (1H, d, $J=9.0$ Hz, H-5' ve H-3), 7.35 (1H, t, $J=7.5$ Hz, H-6), 7.53 (1H, t, $J=7.5$ Hz, H-7), 7.83 (1H, d, $J=9.0$ Hz, H-5), 7.75 (1H, d, $J=8.0$ Hz, H-8), 8.15 (1H, d, $J=8.5$ Hz, H-4), 9.32 (1H, brd.s, -CH=N-), 15.04 (1H, brd.s, naphtholic -OH). ¹³C NMR (400 MHz, CDCl₃): δ 21.2 (-CH₃), 91.3 (C-6'), 109.2 (C-1), 119.2 (C-3), 119.3 (C-2'), 120.7 (C-8), 123.7 (C-6), 127.5 (C-4a), 128.9 (C-4'), 129.4 (C-5), 133.0 (C-8a), 136.0 (C-4), 139.3 (C-5'), 139.8 (C-3'), 148.7 (C-1'), 157.3 (-CH=N-), 165.9 (C-2).

1-[(2-iodo-4-methylphenyl)imino]methyl-2-naphthol (2e). Yield: 41.8%. mp: 142 °C. Mass spectra: $m/z = M^+$ [387.0], [259.0 (M-HI, 36.1%)]⁺, [106.1 (C₈H₁₀, 100%)]⁺. Anal: Calcd for C₁₈H₁₄INO (387.21): C, 55.83; H, 3.64; N, 3.62. Found: C, 54.10; H, 3.69; N, 3.41. IR (KBr) ν_{\max} : 3438, 1625, 1574-1497 cm⁻¹. UV (EtOH) $\lambda_{\max}(\log \epsilon)$: 287.6 (0.970), 312.8 (0.779), 366.4 (0.562), 442.4 (0.207), 463.6 (0.196) nm. ¹H-NMR (400 MHz, CDCl₃): δ 2.36 (3H, s, -CH₃), 7.15 (1H, d, $J=7.5$ Hz, H-2'), 7.20 (1H, d, $J=9.0$ Hz, H-5'), 7.24 (1H, d, $J=7.5$ Hz, H-3), 7.32 (1H, t, $J=7.5$ Hz, H-6), 7.50 (1H, t, $J=7.5$ Hz, H-7), 7.73 (1H, s, H-3'), 7.75 (1H, d, $J=8.5$ Hz, H-8), 7.79 (1H, d, $J=9.0$ Hz, H-5), 8.10 (1H, d, $J=8.5$, H-4), 9.29 (1H, brd.s, -CH=N) 15.06 (1H, brd.s, naphtholic -OH). ¹³C NMR (400 MHz, CDCl₃): δ 20.4 (-CH₃), 95.6 (C-6'), 109.2 (C-1), 117.9 (C-2'), 119.1 (C-3), 120.6 (C-8), 123.6 (C-6), 127.7 (C-4a), 127.9 (C-7), 129.3 (C-5), 130.2 (C-5'), 132.9 (C-8a), 135.8 (C-4), 138.2 (C-4'), 139.9 (C-3'), 146.4 (C-1'), 156.8 (-CH=N-), 165.5 (C-2). HETCOR (CDCl₃): 9.29, -CH=N- (156.8, -CH=N- azomethine carbon), 8.10, H-4 (135.8, C-4), 7.75, H-8 (120.6, C-8), 7.73, H-3' (139.9, C-3'), 7.79, H-5 (129.3, C-5), 7.50, H-7 (127.9, C-7), 7.32, H-6 (123.6, C-6), 7.20, H-5' (130.2, C-5'), 7.24, H-3 (119.1, C-3), 7.15, H-2' (117.9, C-2').

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