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Synthesis of Iodinated Naphthoquinones Using Morpholine-Iodine Complex

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ABSTRACT

The efficient synthesis of 2-hydroxy-3-iodo-1,4-naphthoquinone (**3**), 2-amino-3-iodo-1,4-naphthoquinone (**4**), and 2-iodo-1,4-naphthoquinone (**5**) have been developed using the parent naphthoquinone in combination with the charge-transfer complex between iodine and morpholine.

Key Words: Iodination; Lawsone; Morpholine-iodine complex; Naphthoquinones.

INTRODUCTION

Recently, iodinated arenes or heteroarenes have become some of the most important intermediates in the synthesis of natural products or pharmaceutical

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drugs; for a review on the preparation and uses of iodoarenes, see Ref.^[1]. For example, iodobenzene derivatives can undergo carbon-carbon cross-coupling reactions such as the Sonogashira,^[2] Heck,^[3] Stille,^[4] and Suzuki^[5] reactions catalyzed by palladium. In these reactions, the presence of iodine facilitates the palladium insertion into the C-X bond to a greater degree than bromine or chlorine. However, the availability of iodinated arenes is limited by the lower electrophilicity of iodine compared to the other halogens. Furthermore, the preparation of iodinated compounds frequently requires the use of strong acids (e.g., HNO₃),^[6] oxidizing agents (e.g., NaOCl),^[7] or heavy metals salts (e.g., Hg²⁺),^[8] which can create problems with sensitive substrates and complicate the conditions of the reaction and during isolation of the product. More expensive (and highly water-sensitive) reagents such as ICI,^[9] diiodine pentoxide (I₂O₅),^[10] and *N*-iodosuccinimide^[11] have been developed for specific iodinations.

We are interested in the synthesis of naphthoquinone compounds and have been exploring the various carbon-carbon cross-coupling reactions to form alkylated derivatives. Of the various iodination methods utilized for arenes, several procedures were applied to the formation of halogenated naphthoquinones.^a One reagent seemingly forgotten for this type of transformation is the charge-transfer complex between morpholine and iodine.^[12] In this report, we present our results using this morpholine-iodine complex (**2**) for the efficient and practical preparation of various iodinated naphthoquinones.

RESULTS AND DISCUSSION

The morpholine-iodine complex (prepared as an isolable solid^[12a] or in situ^[12b,12d]) is known to react with activated arenes (phenols and arylamines) to perform successful iodinations where other reagents fail. However, only anhydrous organic solvents (alcohols, ether, benzene) have been investigated up to this point due to the known instability of the charge-transfer complex in the presence of water.^[12a] We have discovered that the reaction between lawsone (2-hydroxy-1,4-naphthoquinone, **1**) and the complex provides in good yield 2-hydroxy-3-iodo-1,4-naphthoquinone (For previous synthesis of compound **3** (in lower field) see Ref.^[13]), in a variety of solvents (e.g., methanol, ethyl acetate, benzene). More interesting is that the complex, if added in small portions over time, can be used in

^aWe have found that naphthoquinones cannot be halogenated in high yields under oxidative conditions (decomposition) nor in the presence of metal ions (formation of chelates). The iodination does not go to completion using only elemental iodine (even in large excess).

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water on the benchtop with no particular precautions to exclude oxygen from the reaction flask. The iodination proceeds without concomitant decomposition of the complex if the pH of the solution is basic. Since these conditions are illustrative of "green chemistry," we foresee the wide use of this reagent on an industrial scale. The use of water appears to accelerate the reaction and provides the advantage of easy isolation: after acidification, the product precipitates from the aqueous solution and can be filtered off. The importance of 2-hydroxy-3-iodo-1,4-naphthoquinone in the synthesis of naphtha[2,3b]furan-4,9-dione natural products has been demonstrated by Kobayashi (see Fig. 1).^[14]

The same procedure can be applied to the preparation in good yield of 2-amino-3-iodo1,4-naphthoquinone from aminonaphthoquinone. In this case, the reaction is more heterogeneous due to the low solubility of amino-naphthoquinones in aqueous solution. However, the work-up procedure is equally facile: acidification of the aqueous solution allows the easy filtration of the product away from the impurities (see Fig. 2).

We believe that in the charge-transfer complex the central iodine atom is activated to nucleophilic attack. The pi-nucleophile (lawsone or amino-naphthoquinone) attacks the activated electrophilic iodine faster than sigma-nucleophiles, such as water (see Fig. 3).^[15]

We were curious if the electrophilic nature of the iodine complex extended to deactivated alkenes i.e., unsubstituted naphthoquinones (see literature for the iodination of enones: (a) I₂/ceric ammonium nitrate,^[16a] (b) I₂/pyridine,^[16b] (c) I₂/*bis*(tetra-*n*, butylammonium peroxydisulphate,^[16c] (d) I₂/PhI(OCOCF₃)₂.^[16d]). The morpholine-iodine complex has been used with enones to form α,β -dimorpholinyl ketones, but naphthoquinones were not studied. See Ref.^[17]. Specifically, the reaction between 1,4-naphthoquinone and the morpholine-iodine complex did not form any iodination product in most solvents, including water. However, when an excess of reagent (>2 equivalents) was used in refluxing dichloroethane, the substrate was completely consumed and two products were formed: 2-morpholinyl-1,4-naphthoquinone and 2-iodo-1,4-naphthoquinone. (For previous syntheses of compound **5** (in lower yield), see Ref.^[18]) (see Fig. 4).



Figure 1.



The mechanism of this reaction is different from the reaction with activated naphthoquinones; we believe that the complex dissociates under the conditions of the reaction, the morpholine reacts with the 1,4-naphthoquinone in a Michael-like attack, and the enolate formed reacts with free iodine. From this intermediate, a second equivalent of morpholine deprotonates either of the α -protons to eliminate morpholine or iodide to provide either product. Although a mixture is formed, the two products are easily separated by column chromatography to provide both compounds in a pure state. We are continuing to investigate this reaction to search for conditions that lead to a higher selectivity. Albeit the limitations, at this point the indicated transformations are the most direct and economical preparations of iodinated naphthoquinones (see Fig. 5).

EXPERIMENTAL

The morpholine-iodine complex was prepared according to Ref.^[12a] and was stored in a desiccator protected from light. Lawsone and 1,4-naphthoquinone are commercial compounds and are used as received. 2-Amino-1,4-naphthoquinone was prepared by the procedure of Couladouros.^[19] NMR spectra were recorded on a Varian 400-MHz spectrometer in CDCl₃. All IR spectra were recorded on a Perkin-Elmer Spectrum 1000.



Figure 3.

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Figure 4.

2-Hydroxy-3-iodo-1,4-naphthoquinone (3): To a mixture of lawsone (174 mg, 1.00 mmol) and K₂CO₃ (420 mg, 3.00 mmol) in an Erlenmeyer flask was added distilled water (10 mL). The dark red solution was stirred at room temperature while the morpholine-iodine complex (425 mg, 1.25 mmol) was added in small portions every 15 min during 2 hr. The reaction was stirred at room temperature for an additional hour and then the mixture was filtered to remove any solids present. The filtrate was cooled in an ice bath and then acidified with 25% H₃PO₄ until the pH was approximately 2. At this point, the mixture was allowed to age (10-60 min) to eliminate any complex remaining and to form a bright yellow precipitate. The solid was filtered off and washed with cold H2O. The product was dried under vacuum overnight to provide the desired hydroxyiodo product 3 (261 mg, 87%). This product was pure (>98%) by analysis of the 1 H NMR spectrum but can be recrystallized in glacial acetic acid and then dried to form analytically pure crystals. m.p. 177°C-179°C (lit. m.p.^[13d] 177°C-179°C) UV (EtOH): λ 202, 252 (max), 285 (sh), 330, 404 nm IR: 3196 (br), 1671, 1646, 1621, 1579, 1293, 1258 (s), 1212, 1120, 999, 778, 718, 678 cm⁻¹.



¹H-NMR: 8.14 (1H, dd, J = 8.0, 2.0 Hz) H5/H8, 8.08 (1H, dd, J = 8.0, 2.0 Hz) H5/H8, 8.04 (1H, bs) OH; 7.78 (1H, td, J = 8.0, 2.0 Hz) H6/H7, 7.74 (1H, td, J = 8.0, 2.0 Hz) H6/H7 ¹³C-NMR: 178.75 (C4), 177.26 (C1), 159.51 (C2), 142.25 (C3), 135.12 (C6/C7), 133.44 (C6/C7), 131.77 (C4a/C8a), 128.77 (C4a/C8a), 128.15 (CS/C8), 127.01 (CS/C8).

2-Amino-3-iodo-1,4-naphthoguinone (4): To a mixture of 2-amino-1,4naphthoquinone (246 mg, 2.00 mmol) and K₂CO₃ (829 mg, 6.00 mmol) in an Erlenmeyer flask was added distilled water (20 mL). The orange suspension was stirred at room temperature while the morpholine-iodine complex (820 mg, 2.4 mmol) was added in small portions every 15 min during 2 hr. The reaction was stirred at room temperature for an additional hour. The reaction mixture was cooled in an ice bath and then acidified with 25% H₃PO₄ until the pH was approximately 4. The solid was filtered off, washed with cold dilute NaHSO₃ solution to remove any residual iodine, and finally washed with cold H_2O . The product was dried under vacuum overnight to provide the desired aminoiodo product 4 (508 mg, 85%). This product was pure (> 98%) by analysis of the ¹H NMR spectrum but can be recrystallized in distilled water and then dried to form analytically pure orange crystals. m.p. 201°C-202°C. UV (EtOH): λ 202, 215, 230, 264 (max), 322 (sh), 456 nm IR: 3450, 3346, 1676, 1604 (s), 1577 (s), 1365, 1270 (s), 721, 677 cm⁻¹ ¹H-NMR: 8.16 (1 H, dd, J = 2.4, 8.8 Hz) H5/H8, 8.07 (1 H, dd, J = 2.4, 8.8 Hz) H5/H8,7.71 (ddd, J = 2.4, 8.8, 9.6 Hz) H6/H7, 7.66 (1 H, ddd, J = 2.4, 8.8, 9.6 Hz) H6/H7, 5.2 (2H, brs) NH2 ¹³C-NMR: 177.44 (C4), 177.18 (C1), 151.20 (C2), 134.74 (C6/C7), 132.68 (C6/C7), 132.01 (C4a/C8a), 129.54 (C4a/C8a), 127.61 (C5/C8), 126.83 (C5/C8), 85.76 (C3).

2-Iodo-1,4-naphthoquinone (5): A solution of 1,4-naphthoquinone (158 mg, 1.00 mmol) and dichloroethane (10 mL) in a round-bottomed flask was heated to 60°C under a nitrogen atmosphere to form a yellow solution. The morpholine-iodine complex (1.02 g, 3.00 mmol) was added and the red reaction mixture was heated to reflux for 1 hr. At this time, analysis of the thin layer chromatography (TLC) indicated that there was no naphthoquinone remaining. The reaction mixture was concentrated in vacuo and the resulting residue was applied to the top of a silica chromatography column. Elution with toluene provided fractions of the iodo product 5 and then elution with toluene-ethyl acetate (4:1) provided fractions of the morpholine product 6. The fractions containing 5 were combined and the dissolvent was removed in vacuo to provide product contaminated by a dark residue. Recrystallization from hexane provided analytically pure iodonaphthoquinone (100 mg, 35%) as bright-orange crystals. m.p. 119°C-120°C (lit. m.p.^[18a] 119°C-120°C) UV (EtOH): λ 210 (max), 244, 288, 333 nm IR: 3048, 1651 (s), 1586 (s), 1567 (s), 1327, 1299 (s), 1247 (s), 1223, 1118, 910, 808, 777, 691, 666 cm⁻¹.

¹H-NMR: 8.16–8.19 (1H, dd, J = 8.0, 2.0 Hz) H5/H8, 8.07–8.10 (1H, dd, J = 8.0, 2.0 Hz) H5/H8, 7.79 (1H, td, J = 8.0, 2.0 Hz) H6/H7, 7.75 (1 H, td, J = 8.0, 2.0 Hz) H6/H7, 7.95 (1H, s) H3.

¹³C-NMR: 181.77 (C4), 178.52 (C1), 148.23 (C3), 134.17 (C6/C7), 133.82 (C6/C7), 131.59 (C4a/C8a), 129.54 (C4a/C8a), 128.05 (C5/C8), 126.88 (C5/C8), 122.91 (C2).

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REFERENCES

- Merkushev, E.B. Advances in the synthesis of iodoaromatic compounds. Synthesis 1988, 923–937.
- (a) Sonogashira, K. *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, L., Eds.; Pergamon Press: New York, 1991; Vol. 3, 521–549;
 (b) Sonogashira, K. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P.J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; 203–229.
- Beletskaya, I.P.; Cheprakov, A.V. The heck reaction as a sharpening stone of palladium catalysis. Chem. Rev. 2000, 100, 3009–3066.
- Stille, J.K. *The Stille Reaction*. Farina V.; Krrshr Scott, W.J., Eds.; John Wiley & Sons: New York, 1998.
- Miyaura, N.; Suzuki, A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. Chem. Rev. 1995, 95, 2457–2483.
- Dains, F.B.; Brewster, R.Q. Iodobenzene. In Organic Synthesis Collected, Vol. 1; John Wiley and Sons: New York, 1932, 323–324.
- Edgar, K.J.; Falling, S.N. An efficient and selective method for the preparation of iodophenols. J. Org. Chem. 1990, 55, 5287–5291.
- Orito, K.; Hatakeyama, T.; Takeo, M.; Suginome, H. Iodination of alkyl aryl ethers by mercury(II) oxide-iodine reagent in dichloromethane. Synthesis 1995, 1273–1277.
- (a) Wariishi, K.; Morishima, S.; Inagaki, I. Facile synthesis of 1,4dialkoxy-2,5-diiodobenzenes: reaction of dialkoxybenzenes with iodine monochloride in alcoholic solvent. Org. Process Res. Dev. 2003, 7, 98–100; (b) Hubig, S.M.; Jung, W.; Kochi, J.K. Cation radicals as intermediates in aromatic halogenation with iodine monochloride: solvent and

salt effects on the competition between chlorination and iodination. J. Org. Chem. **1994**, *59*, 6233–6244.

- 10. Brazdil, L.C.; Cutler, C.J. Selective production of diiodobenzene and iodobenzene from benzene. J. Org. Chem. **1996**, *61*, 9621–9622.
- (a) Castanet, A.-S.; Colobert, F.; Broutin, P.-E. Mild and regioselective iodination of electro-rich aromatics with *N*-iodosuccinimide and catalytic trifluoroacetic acid. Tetrahedron Lett. **2002**, *43*, 5047–5048;
 (b) Carreño, M.C.; Garcia Ruano, J.L.; Sanz, G.; Toledo, M.A.; Urbano, A. Mild and regiospecific nuclear iodination of methoxybenzenes and naphthalenes with *N*-iodosuccinimide in acetonitrile. Tetrahedron Lett. **1996**, *37*, 4081–4084; (c) Olah, G.A.; Wang, Q.; Sandford, G.; Prakash, G.K.S. Iodination of deactivated aromatics with *N*-iodosuccinimide in trifluoromethanesulfonic acid (NIS-CF₃SO₃H) via in situ generated superelectrophilic iodine(I) trifluoromethanesulfonate. J. Org. Chem. **1993**, *58*, 3194–3195.
- (a) Rice, R.V.; Beal, G.D. Morpholine periodide. US Patent 2,290,710, July 21, 1942. (b) Chabrier, P.; Seyden-Penne, J.; Fouace, A.-M. Compt. Rend. Acad. Sci. **1957**, 245, 174; (c) Southwick, P.L.; Kirchner, J.R. The morpholine-iodophenylacetylene adduct or chargetransfer complex. Formation and conversion to *N*-styrylmorpholine. J. Org. Chem. **1962**, 27, 3305–3308; (d) Giza, C.A.; Hinman, R.L. New thyroxine analogs. Halogen derivatives of 3-carbethoxy-5hydroxy-2-methylbenzofuran. J. Org. Chem. **1964**, 29, 1453–1461.
- (a) Kehrmann, R.; Mascioni, B. Ber. Dtsch. Chem. Ges. 1895, 28, 345;
 (b) Courseille, C.; Geoffre, S.; Schvoerer, M. Crystal structure of 2-hydroxy-3-iodo-1,4 naphthoquinone. Compt. Rend. Acad. Sci. 1971, 273, 1633–1634;
 (c) Sharma, J.; Singh, P.K.; Singh, K.P.; Khanna, R.N. Iodination of naphthoquinones and coumarin catalyzed by ceric ammonium and mercuric nitrates. Org. Prep. Proced. Int. 1995, 27, 84–86;
 (d) Hatzigrigoriou, E.; Spyroudis, S.; Varvoglis, A. Derivatives of 1,4-naphthoquinone via 3-(phenyliodonio)-1,2,4-trioxo-1,2,3,4-tetra-hydronaphthalenide. Liebigs Ann. Chem. 1989, 167–170.
- Kobayashi, K.; Uneda, T.; Kawakita, M.; Morikawa, O.; Konishi, H. Onepot synthesis of naphtho[2,3-b]furan-4,9-diones by sequential coupling/ ring closure reactions. Tetrahedron Lett. **1997**, *38*, 837–840.
- Mayr, H.; Kempf, B.; Ofial, A.R. π-Nucleophilicity in carbon-carbon bond-forming reactions. Acc. Chem. Res. 2003, 36, 66–77.
- 16. (a) Zhang, F.; Li, Y. A new and efficient synthesis of 3-iodo derivatives of flavones, thioflavones, and thiochromones. Chin. Chem. Lett. 1991, 2, 763–764; (b) Johnson, C.R.; Adams, J.P.; Braun, M.P.; Senanayake, C.B.W.; Wovkulich, P.M.; Uskokovic, M.R. Direct α-iodination of cycloalkenones. Tetrahedron Lett. 1992, 33, 917–918;

Synthesis of Iodinated Naphthoquinones

(c) Bovonsombat, P.; Angara, G.J.; McNelis, E. Concerning the formations of α -iodoenones. Tetrahedron Lett. **1994**, *35*, 6787–6790; (d) Djuardi, E.; Bovonsombat, P.; McNelis, E. Formations of α -iodoenones by iodine and catalytic amounts of amines. Syn. Commun. **1997**, *27*, 2497–2503; (e) Whang, J.P.; Yang, S.G.; Kim, Y.H. Novel α -iodination of functionalized ketones with iodine mediated by *bis* (tetra-*n*-butylammonium) peroxydisulfate. J. Chem. Soc., Chem. Commun. **1997**, 1355–1356; (f) Benhida, R.; Blanchard, P.; Fourrey, J.-L. A mild and effective iodination method using iodine in the presence of *bis*-(trifluoroacetoxy)iodobenzene. Tetrahedron Lett. **1998**, *39*, 6849–6852.

- (a) Southwick, P.L.; Christman, D.R. Reactions of unsaturated compounds with iodine-amine complexes. I. Reactions of benzalaceto-phenone and benzalacetone. J. Am. Chem. Soc. 1952, 74, 1886–1891;
 (b) Southwick, P.L.; Christman, D.R. Reactions of iodine-amine complexes with unsaturated compounds. II. An investigation of the scope of the reaction with the iodine-morpholine complex. J. Am. Chem. Soc. 1953, 75, 629–632.
- (a) Hodgson, H.H.; Elliott, R.L. J. Chem. Soc. 1935, 1850–1854;
 (b) Gautier, J.; Hauw, C.; Housty, J.; Schvoerer, M. Molecular crystal structure of 2-iodo-1,4-naphthoquinone. Compt. Rend. Acad. Sci. 1971, 273, 956–958;
 (c) Sharma, J.; Singh, P.K.; Singh, K.P.; Khanna, R.N. Iodination of naphthoquinones and coumarin catalyzed by ceric ammonium and mercuric nitrates. Org. Prep. Proced. Int. 1995, 27, 84–86.
- Couladouros, E.A.; Plyta, Z.F.; Haroutounian, S.A.; Papageorgiou, V. Efficient synthesis of aminonaphthoquinones and azidobenzohydroquinones: mechanistic considerations of the reaction of hydrazoic acid with quinones. an overview. J. Org. Chem. 1997, 62, 6–10.

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