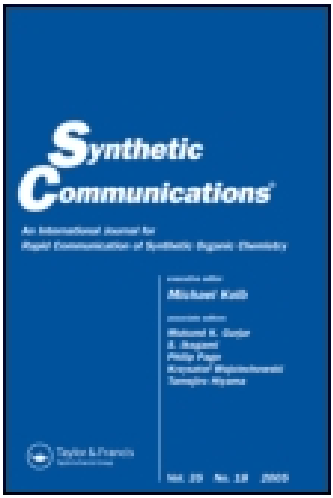

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Facile Iodine(III)-Mediated Approach for the Regioselective Chlorination of 2-Aryl-2,3-dihydro-4(1*H*)-quinolones

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Abstract: Oxidation of 2-aryl-2,3-dihydro-4(1*H*)-quinolones (**1**) with 1.5 equivalents of (dichloroiodo)benzene in dichloromethane at room temperature leads to regioselective chlorination, thereby offering an efficient method for the synthesis of new 2-aryl-6-chloro-2,3-dihydro-4(1*H*)-quinolones (**3**).

Keywords: 2-Aryl-2,3-dihydro-4(1*H*)-quinolones, (dichloroiodo)benzene, regioselective chlorination

INTRODUCTION

The introduction of chlorine into an aromatic ring is a commonly used reaction in organic synthesis and medicinal chemistry. Several methods for chlorination have been reported in literature.[1–3] However, most of these still suffer from serious shortcomings such as the formation of by-products and poor selectivity of the reaction. Among several chlorinating agents, we directed our attention to (dichloroiodo)benzene because of its low toxicity, easy handling, and relatively benign nature.[4] Moreover, the use of (dichloroiodo)benzene for large-scale monochlorination of 4-aminoacetophenone has been previously described.[5] As a part of our ongoing interest in the development of iodine(III)-mediated methods

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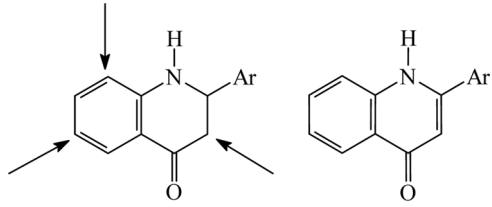
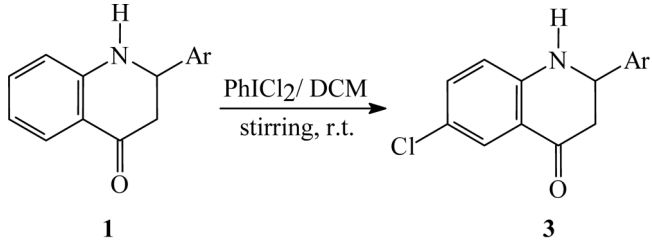
especially for the synthesis of heterocyclic compounds,[6–12] we now became interested in the scope of (dichloroiodo)benzene-mediated nuclear chlorination. In this context, the opportunity was taken to examine the reaction of 2-aryl-2,3-dihydro-4(1*H*)-quinolones (**1**) with (dichloroiodo)benzene in dichloromethane at room temperature. The reagent, in principle, could chlorinate C(3), C(6) (*para* to –NH), and C(8) (*ortho* to –NH) of 2-aryl-2,3-dihydro-4(1*H*)-quinolone (**1**). In addition, we also considered the possibility that the initially formed C(3)-chloro product could undergo elimination of one molecule of HCl to give quinolone of the type **2**.



1 **2**

To determine the feasibility of such possibilities, we first carried out the reaction of **1a** with 1.5 equivalents of (dichloroiodo)benzene in dichloromethane at room temperature. Interestingly, the reaction afforded a solid product, which was characterized as 6-chloro-2,3-dihydro-2-phenyl-4(1*H*)-quinolone (**3a**) on the basis of physical and spectral data. The IR spectrum displayed carbonyl stretch and –NH stretch at 1657 and 3347 cm^{-1} respectively. The ^1H NMR spectrum of **3a** showed a characteristic doublet at 7.77 ppm with a coupling constant of 2.4 Hz that can be ascribed to the C_5-proton. A doublet with *meta* interaction clearly confirmed the presence of a chloro group at the sixth position. Mass spectrum showed M^+ and $M^+ + 2$ peaks in relative abundance, 3:1, clearly confirming the presence of one chlorine atom in the structure of product. The regioselective chlorination that occurred in this reaction is a significant result, as the compounds of type **3** are unknown in the literature. The generality of this facile transformation was established by treating other 2,3-dihydro-4(1*H*)-quinolones (**1b–f**) with (dichloroiodo)benzene under similar conditions which provided 2-aryl-6-chloro-2,3-dihydro-4(1*H*)-quinolones (**3b–f**) in good yields (53–76%) (Scheme 1).[13]

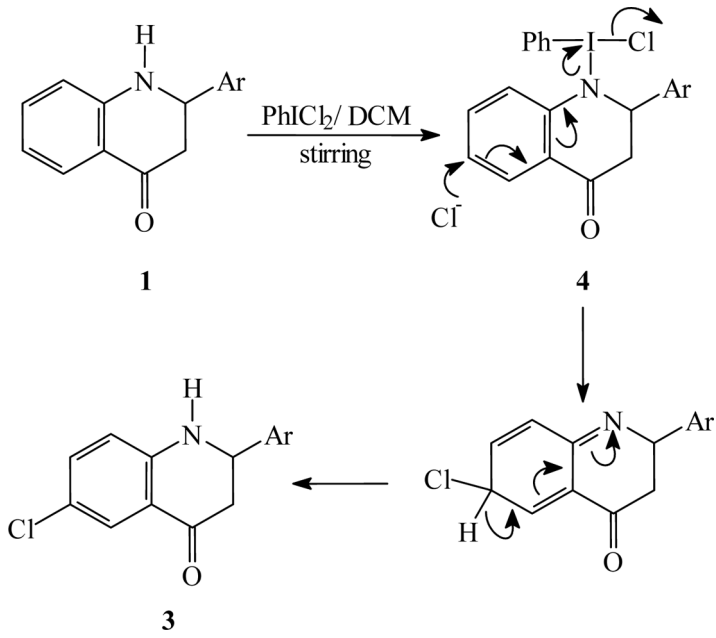
The mechanism of the reaction is not clear. A plausible pathway for transformation **1** → **3** is outlined in Scheme 2. The transformation probably involves the formation of N-I(III) intermediate **4** by ligand exchange between –NH group and (dichloroiodo)benzene. The N-I(III)



1 3

1,3	Ar
a	C_6H_5
b	4-$OMeC_6H_4$
c	2-$OMeC_6H_4$
d	4-ClC_6H_4
e	4-BrC_6H_4
f	4-$NO_2C_6H_4$

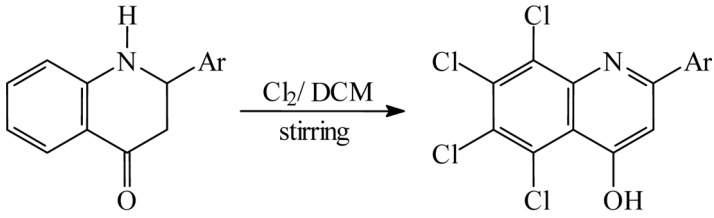
Scheme 1. Regioselective chlorination of 2-aryl-2,3-dihydro-4(1*H*)-quinolones using $PhICl_2$.



Scheme 2. Mechanistic pathway for chlorination.

intermediate **4** might give the product by nucleophilic attack of chloride ion with simultaneous reductive elimination of iodobenzene.

To determine whether the reaction proceeds through the in situ generation of chlorine from (dichloroiodo)benzene, we performed chlorination of a representative case **1e** with chlorine gas. In this experiment, the chlorine gas was passed through solution of **1e** in dichloromethane for 2 h. Surprisingly, the reaction afforded a polysubstitution product, 2-(4′-bromophenyl)-5,6,7,8-tetrachloro-4-hydroxyquinoline (**5e**) [Eq. (1)].



1e **5e**

This experiment clearly indicated that regioselective chlorination occurring with (dichloroiodo)benzene does not proceed through the in situ generation of chlorine from the reagent.

The iodine(III)-mediated conversion **1** → **3**, a new application of (dichloroiodo)benzene, is significant for the following reasons:

1. The method involves mild conditions and simple experimentation.
2. The reaction offers an easy and efficient way for selective nuclear monochlorination of 2-aryl-2,3-dihydro-4(1*H*)-quinolones at the sixth position.
3. All the chlorodihydroquinolones **3a-3f,** synthesized in this study, are new compounds.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer IR 1800 spectrophotometer. The ^{1}H NMR spectra were recorded on Brucker 300-MHz instrument. 2-Aryl-2,3-dihydro-4(1*H*)-quinolones (**1**) were synthesized according to literature procedures.[14–16]

Preparation of 6-Chloro-2-aryl-2,3-dihydro-4(1*H*)-quinolones (3) According to Scheme 1

(Dichloroiodo)benzene (0.825 g, 0.003 mol) was added to a solution of 2-phenyl-2,3-dihydro-4(1*H*)-quinolone **1a** (0.446 g, 0.002 mol) in dichloromethane (20 ml), in portions and the resulting mixture was allowed to stir for 2 h at room temperature. The reaction mixture was concentrated on a water bath. The residue was purified by column chromatography on silica gel (100–200 mesh) using petroleum ether–ethyl acetate as eluent to give 0.380 g of **3a**. Other derivatives **3b–3f** were prepared in a similar manner.

Data

6-Chloro-2-phenyl-2,3-dihydro-4(1*H*)-quinolone (**3a**)

Yield 74%, mp 156–58 °C; IR (ν_{max}, in KBr): 1657, 3347 $cm^{-1;}$ ^1H NMR ($CDCl_3$, 300 MHz, δ): 2.68–2.86 (m, 2H), 4.4–4.5 (bp, 1H, NH), 4.67 (dd, 1H, C_2-H, $J = 13.2$ Hz, 4.5 Hz), 6.60 (d, 1H, $J = 8.7$ Hz), 7.22–7.39 (m, 6H), 7.77 (d, 1H, C_5-H, $J = 2.4$ Hz). Elemental analysis: found C, 69.5%; H, 4.5%; N, 5.2%; requires C, 70%; H, 4.7%; N, 5.4%. Mass: 257 (M^+), 259 ($M^+ + 2$).

6-Chloro-2-(4′-methoxyphenyl)-2,3-dihydro-4(1*H*)-quinolone (**3b**)

Yield 68%, mp 98–100 °C; IR (ν_{max}, in KBr): 1658, 3348 $cm^{-1;}$ ^1H NMR ($CDCl_3$, 300 MHz, δ): 2.7–2.9 (m, 2H), 3.76 (s, 3H, $-OCH_3$), 4.65 (dd, 1H, C_2-H, $J = 13.2$ Hz, 4.5 Hz), 4.9–5.0 (bp, 1H, NH), 6.86–6.89 (m, 2H), 7.22–7.37 (m, 4H), 7.71 (d, 1H, C_5-H, $J = 2.4$ Hz). Elemental analysis: found C, 65.8%; H, 4.6%; N 4.2%; requires C, 66.9%; H, 4.9%; N 4.9%. Mass: 287 (M^+), 289 ($M^+ + 2$).

6-Chloro-2-(2′-methoxyphenyl)-2,3-dihydro-4(1*H*)-quinolone (**3c**)

Yield 53%, mp 88–90 °C; IR (ν_{max}, in KBr): 1660, 3345 $cm^{-1;}$ ^1H NMR ($CDCl_3$, 300 MHz, δ): 2.79–3.00 (m, 2H), 3.76 (s, 3H, $-OCH_3$), 4.5–4.7 (bp, 1H, NH), 5.15 (dd, 1H, C_2-H, $J = 13.2$ Hz, 4.5 Hz), 6.8–7.0 (m, 2H), 7.25–7.30 (m, 1H), 7.34–7.40 (m, 1H), 7.55–7.65 (m, 2H), 7.70 (d, 1H, C_5-H, $J = 2.4$ Hz). Elemental analysis: found C, 65.2%; H, 4.3%; N, 4.4%; requires C, 66.9%, H, 4.9%; N, 4.9%. Mass: 287 (M^+), 289 ($M^+ + 2$).

6-Chloro-2-(4′-chlorophenyl)-2,3-dihydro-4(1*H*)-quinolone (**3d**)

Yield 70%, mp 177–178 °C; IR (ν_{max}, in KBr): 1658, 3343 $cm^{-1;}$ ^1H NMR ($CDCl_3$, 300 MHz, δ): 2.71–2.81 (m, 2H), 4.4–4.5 (bp, 1H, NH), 4.66 (dd, 1H, C_2-H, $J = 13.2$ Hz, 4.5 Hz), 6.60 (d, 1H, $J = 8.7$ Hz), 7.20–7.24 (m, 1H), 7.32–7.39 (m, 4H), 7.76 (d, 1H, C_5-H, $J = 2.4$ Hz). Elemental analysis: found C, 60.8%; H, 3.3%; N, 4.4%; requires C, 61.8%; H, 3.8%, N, 4.8%. Mass: 291 (M^+), 293 ($M^+ + 2$), 295 ($M^+ + 4$).

6-Chloro-2-(4′-bromophenyl)-2,3-dihydro-4(1*H*)-quinolone (**3e**)

Yield 76%, mp 180–81 °C; IR (ν_{max}, in KBr): 1658, 3343 $cm^{-1;}$ ^1H NMR ($CDCl_3$, 300 MHz, δ): 2.75–2.89 (m, 2H), 4.3–4.5 (bp, 1H, NH), 4.73 (dd, 1H, C_2-H, $J = 13.2$ Hz, 4.5 Hz), 6.70 (d, 1H, $J = 8.7$ Hz), 7.27–7.36 (m, 3H), 7.54–7.57 (m, 2H), 7.85 (d, 1H, C_5-H, $J = 2.4$ Hz); Elemental analysis: found C, 52.9%; H 3.6%; N 3.28%; Requires C 53.5%, H, 3.3%; N, 4.2%; Mass: 335 (M^+), 337 ($M^+ + 2$), 339 ($M^+ + 4$).

6-Chloro-2-(4′-nitrophenyl)-2,3-dihydro-4(1*H*)-quinolone (**3f**)

Yield 66%, mp 188–90 °C; IR (ν_{max}, in KBr): 1348, 1545, 1661, 3349 $cm^{-1;}$ ^1H NMR ($CDCl_3$, 300 MHz, δ): 2.76–2.79 (m, 2H), 4.3–4.5 (bp, 1H, NH), 4.69 (dd, 1H, C_2-H, $J = 13.2$ Hz, 4.5 Hz), 6.6–6.7 (m, 1H), 7.25–7.30 (m, 1H), 7.56–7.61 (m, 2H), 7.78 (d, 1H, C_5-H, $J = 2.4$ Hz), 8.19–8.22 (m, 2H). Elemental analysis: found C, 58.8%; H, 3.6%; N, 8.8%; requires C, 59.6%; H 3.6%; N, 9.3%. Mass: 302 (M^+), 304 ($M^+ + 2$).

Preparation of 2-(4′-Bromophenyl)-5,6,7,8-tetrachloro-4-hydroxyquinoline (**5e**)

Forty mL dry dichloromethane and 2-(4′-bromophenyl)-2,3-dihydro-4(1*H*)-quinolone **1e** (0.604 g, 0.002 mol) were placed in a 100-mL, two-necked, round-bottom flask with an inlet tube for the introduction of chlorine gas and an exit tube carrying calcium chloride guard tube. The flask was cooled in an ice–salt mixture, and dry chlorine gas was passed through a stirred solution of **1e** in dichloromethane for 2 h. The reaction mixture was concentrated on a water bath. The residue was purified by column chromatography on silica gel (100–200 mesh) using petroleum ether–ethyl acetate as eluent.

Yield 71%, mp 204–206 °C; IR (ν_{max}, in KBr): 3243 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.58 (d, 2H, $J = 8.8$ Hz), 7.76 (d, 2H, $J = 8.8$ Hz),

7.84 (s, 1H), 8.4 (bp, 1H, −OH). Elemental analysis: found C, 40.8%; H 1.32%; N, 2.9%; requires C, 41.09%; H, 1.37%; N, 3.2%; Mass: 435 (M^+), 437 ($M^+ + 2$), 439 ($M^+ + 4$), 441 ($M^+ + 6$).

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REFERENCES

1. McBee, E. T.; Hass, H. B. Developments in the chlorination of satrurated hydrocarbons. *Ind. Eng. Chem.* **1943**, *33*, 137.
2. Neale, R. S.; Sehepers, R. G.; Walsh, M. R. The chlorination of reactive anilines. *J. Org. Chem.* **1964**, *29*, 3390.
3. Nilkson, T. E.; Roche-Dolson, C. A. A convenient procedure for the chlorination of deactivated anilines. *Synthesis* **1985**, 669.
4. (a) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*, Academic Press: London, 1997; (b) Skulski, L.; Organic iodine (I, II, V) chemistry: 10 years of developments at the medical university of Warsaw, Poland. *Molecules* **2000**, *5*, 1331; (c) Zhdankin, V.V.; Stang, P.J. Developments in the Chemistry of Polyvalent Iodine Compounds. *Chem. Rev.* **2002**, *102*, 2523; (d) Zhdankin, V. V. *Encyclopedia of Reagents for Organic Synthesis*. Paquette, L. A. Ed., Johnz Wiley & Sons, Ltd.: Chichester, England, 2004.
5. Zanka, A.; Takeuchi, H.; Kubota, A. Large-scale preparation of iodobenzene dichloride and efficient monochlorination of 4-aminoacetophenone. *Org. Process Res. Devel*. **1998**, *2*, 270–273.
6. Prakash, O.; Batra, A.; Sharma, V.; Saini, R. K.; Verma, R. S. Hypervalent iodine(III) mediated synthesis of 2-substituted benzoxazoles. *J. Ind. Chem. Soc.* **2003**, *80*, 1031–1033.
7. Prakash, O.; Sharma, P. K.; Saini, N. Hypervalent iodine reagents in the synthesis of heterocyclic compounds. *Synlett* **1994**, 221–227.
8. Prakash, O.; Batra, H.; Kaur, H.; Sharma, P. K.; Sharma, V.; Singh, S. P.; Moriarty, R. M. Hypervalent iodine oxidative rearrangement of anthranilamides, salicylamides, and some p-substituted amides: A new and convenient synthesis of 2-benzimidazolones, 2-benzoxazolones, and related compounds. *Synthesis* **2001**, 541.

9. Sadana, A.; Mirza, Y.; Aneja, K. R.; Prakash, O. Hypervalent iodine–mediated synthesis of 1-aryl/hetryl-1,2,4-triazolo[4,3-*a*] pyridines and 1-aryl/hetryl 5-methyl-1,2,4-triazolo[4,3-*a*]quinolines as antibacterial agents. *Eur. J. Med. Chem*. **2003**, *38*, 533–536.
10. Prakash, O.; Bhardwaj, V.; Kumar, R.; Tayagi, P.; Aneja, K. R. Organoiodine(III) – mediated synthesis of 3-aryl/hetryl-5,7-dimethyl-1,2,4-triazolo[4,3-a] pyrimidines as antibacterial agents. *Eur. J. Med. Chem*. **2004**, *39*, 1073–1077.
11. Prakash, O.; Kumar, R.; Sharma, D.; Naithani, R.; Kumar, R. Organoiodine(III)-mediated efficient synthesis of new 3,9-diaryl-bis-1,2,4-triazolo[4,3-a][4,3-c]pyrimidines. *Heteroatom Chem*. **2006**, *17*, 653–655.
12. Prakash, O.; Kumar, A.; Sadana, A. K.; Singh, S. P. A novel synthesis of new 3-aryl-7-methylpyrano[4,3-b]pyran-4h,5h-diones using hypervalent iodine(III) reagents. *Synthesis* **2006**, 0021.
13. The studies dealing with the biological activities of 2-aryl-6-chloro-2,3-dihydro-4(1*H*)-quinolones (**3**) are under way and will be published elsewhere.
14. (a) Donnely, J. A.; Farrel, D. F. The chemistry of 2′-amino analogs of 2′-hydroxychalcone and its derivatives. *J. Org. Chem*, **1990**, *55*, 1757. (b) Chalcone derivatives as precursors of 1,2,3,4-tetrahydro-4-quinolones. *Tetrahedron* **1990**, *46*, 885.
15. Tokes, A. L., Litkei, G; Szilagyi, L. N-Heterocycles by cyclization of 2′-Nhr-chalcones, 2′-Nhr-Chalcone Dibromides and 2′-Nhr-α azidochalcones. *Synth. Commun.* **1992**, *22*, 2433.
16. Tokes, A. L.; Forro, I. Bromo-derivatives of 2′-NHR-3,4-methylenedioxy-chalcone and its 4-quinolone isomer. *Synth. Commun.* **1991**, *21*, 1201.