

Iodination of Phenols in Water using Easy to Handle Amine-Iodine Complexes

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A reação entre o iodo e a *N*-metil-piperazina ou a tiomorfolina em água, na presença de KI, levou a formação de complexos amina-iodo estáveis e de fácil manipulação, tal qual o complexo morfolina-iodo, previamente descrito na literatura. Entretanto, o complexo formado entre o iodo e a *N,N*-tetrametiletilenodiamina mostrou-se pouco estável, enquanto que nenhum complexo foi isolado quando a piperidina foi usada como base. Estes resultados mostram que a presença do segundo heteroátomo na estrutura das aminas é fundamental para a formação e estabilidade desses complexos. Neste trabalho descrevemos, pela primeira vez, o emprego dos complexos morfolina-iodo, *N*-metil-piperazina-iodo e tiomorfolina-iodo como agentes de iodação de vários fenóis substituídos, conduzindo a uma série de produtos iodados em rendimentos variando de bons a excelentes.

The reaction between iodo and *N*-methyl-piperazine or thiomorpholine in water, in the presence of KI, led to the formation of stable and easy to handle amine-iodine complexes, as the complex morpholine-iodo previously reported in the literature. However, the complex obtained using *N,N*-tetramethylethylenediamine proved less stable, while no complex was formed when piperidine was used as base. These results show that the presence of a second heteroatom in the structure of amines is of fundamental importance for the formation and stability of these complexes. In this work we describe, for the first time, the use of complexes morpholine-iodo, *N*-methyl-piperazine-iodo and thiomorpholine-iodo as iodinating reagents of several substituted phenols, leading to iodinated products in good to excellent yields.

Keywords: iodophenols, amine-iodine complexes, aromatic iodination, iodinating reagents, *ortho*-iodophenols

Introduction

Aryl iodophenols and other aryl iodides are versatile intermediates in organic synthesis, being used as precursors of new carbon-carbon bonds. These compounds can be used as source of aryl organometallic species as well as substrates for these species in cross-coupling reactions.¹⁻⁹ In particular, the palladium catalyzed oxyarylation of chromens by *ortho*-iodophenols have been used to synthesize pterocarpan and its derivatives.^{10,11} On the other hand, coumarins were formed through a tandem Heck-lactonization reaction when these species were allowed to react with enoates and cinnamates.^{12,13}

Continuing interest of organic chemists in iodination reactions are due to the versatility of iodinated compounds

as building blocks in a variety of synthetic transformations in medicinal chemistry, as well as in the biomedical sciences as imaging agents in non-invasive medical diagnostic techniques due to the possible release of the long-lived radioactive ¹²⁹I isotope.¹⁴⁻¹⁸ In the 1950's the hormone thyroxine and its analogues were prepared as radioiodinated photoprobes.¹⁹⁻²³

A broad range of procedures are described in the literature for the iodination of phenols, involving the use of NIS, ICl, I₂ and iodides salts in the presence of an oxidant, in acid or basic conditions.²⁴⁻³⁴ Recently, Esteves and Mattos³⁵ described the scope of the triiodoisocyanuric (TICA) acid as iodinating agent. The reaction of TICA with activated arenes in acetonitrile led to an efficient and highly regioselective formation of the corresponding iodoarenes. Aniline and phenol were monoiodinated regioselectively using MeOH and CH₂Cl₂ as solvents, respectively.

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Amines can also be used to increase the reactivity of I_2 and Hinman and Giza³⁶ used iodine in the presence of morpholine as iodinating agent to synthesize thyroxine analogs from 3-carbethoxy-5-hydroxy-2-methylbenzofuran. Iodine in the presence of amines react readily with benzophenone, cinnamates and chalcones leading to α,β -diamino-benzylacetophenones and α,β -diamino-benzylacetones derivatives.³⁷ While in most cases complexes of I_2 with amines are generated and used *in situ*,^{13,14} a stable and easily to handle complex **1a** (Figure 1) was prepared by Rice³⁸ just mixing of morpholine, KI and I_2 in water. Recently Perez *et al.*³⁹ described the use of this complex as iodinating reagent to prepare 2-hydroxy-3-iodo-naphthoquinone from lawsone in 87% yield, but did not evaluate the scope of this new iodinating agent using other phenols as substrates.

In this paper we describe the synthesis of new amine-iodine complexes (**1b-d**), structurally related to complex **1a**. The scope of these complexes (**1a-d**) as iodinating agents was evaluated for the first time using a series of phenols (**2-5**) as substrates (Figure 1).

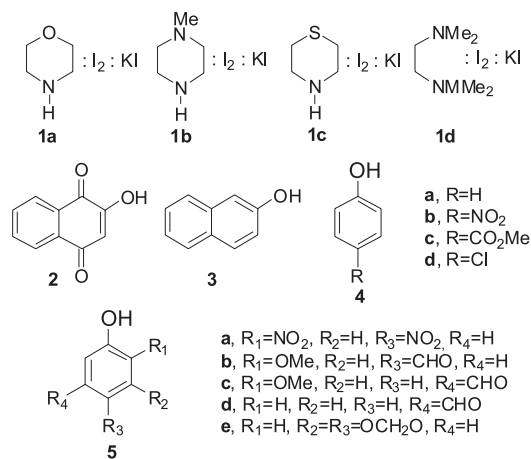
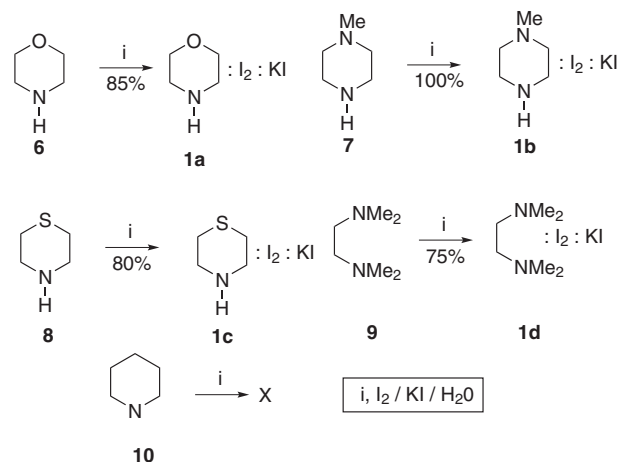


Figure 1. Iodine-amine complexes and phenols studied in this work.

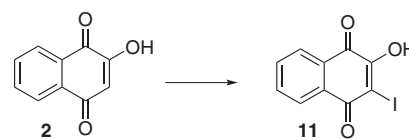
Results and Discussion

A series of secondary amines (**7**, **8** and **10**) and a tertiary amine (**9**) were allowed to react with I_2 in water in the presence of KI, under the conditions described by Rice³⁸ to prepare **1a**. Stable complexes (**1b** and **1c**) were formed when *N*-methyl-piperazine (**7**) and thiomorpholine (**8**) were used (Scheme 1). In contrast, complex **1d**, obtained from *N,N*-tetramethylethylenediamine (**9**), was unstable and completely decomposes at room temperature after 1 h. In contrast, no complex could be isolated from the reaction of I_2 with piperidine (**10**).

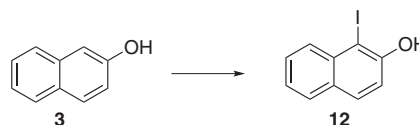


Scheme 1. Synthesis of complexes **1a-d**.

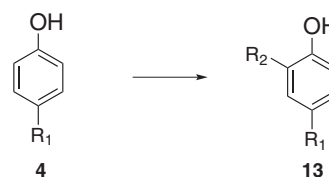
Complexes **1a**, **1b**, **1c** and **1d** were used as iodinating agents of phenols **2-5**. The reactions are shown in Schemes 2, 3, 4 and 5 and yields obtained are shown in Table 1.



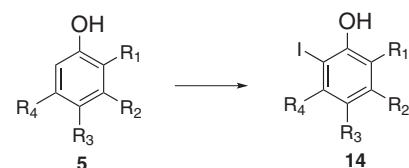
Scheme 2. Iodination of **2** by complexes **1a-d**.



Scheme 3. Iodination of **3** by complexes **1a-d**.



Scheme 4. Iodination of **4a-d** by complexes **1a-d**.



Scheme 5. Iodination of **5a-e** by complexes **1a-d**.

The reaction between complexes **1a-d** (1.2 eq) with lawsone **2** (entries 1-4) gave 3-iodolawsone (**11**) in excellent yields, 87%, 90%, 80%, 80%, respectively. Contrasting to the use of some iodinating agents,^{24,40-42} which in general lead to products of poly-iodination, phenol (**4a**) furnished *para*-iodophenol **13a**²⁴ in good yields by reaction with complexes **1a**, **1b** and **1c** (entries 5-7). We also examined the iodination of the phenols **4b**, **4c** and **4d**, bearing electron withdrawing substituents at the *para* position (NO₂, CO₂CH₃ and Cl) (entries 8-16) and the desired products **13b**,²⁴ **13c**²⁴ and **13d**²⁴ were obtained in good yields by using complexes **1a-d**. However, only starting material was observed when highly deactivated phenol **5a** was allowed to react with complex **1a** (entry 17).

Using the complexes **1a** or **1b**, vanillin **5b** and isovanillin **5c** (entries 18-21), having activating and deactivating groups at the aromatic ring, also led to the corresponding *ortho*-iodophenol derivatives **14b**²⁷ and **14c**,²⁸ although the *para* position in **2h** is not substituted. A mixture of non-identified products was obtained when the *m*-hydroxy-benzaldehyde (**5d**) was treated with the complex **1a** (entry 22). Unfortunately, sesamol **5e**, a very activated phenol, furnished only products of degradation when allowed to react with **1a** (entry 23). α -Naphthol **3** led to **12** in 60% and 63% yield, respectively (entries 24-25), by reaction with complexes **1a** or **1b**.²⁴

Several groups have studied the structure of complexes formed between halogens and interhalogens with *n*-donors.⁴³⁻⁴⁶ According to Manoharan and Ananthavel,⁴⁷ a suitable interaction exist between σ^* -orbital in the interhalogen (LUMO) and lone electron pair of donor (HOMO). The greater the overlap and/or the smaller energy difference between the HOMO of the donor and the LUMO of acceptor, the larger the stabilization energy (Δ), and the greater the extent of mixing, which causes more charge transfer from the donor to the acceptor.⁴⁸⁻⁵²

Amine-iodine complexes have been studied by UV and IR spectroscopy and a dipolar structure has been suggested (Figure 2).^{53,54} Based on our results, the presence of the second hetero-atom in the structure of **1a**, **1b** and **1c**, respectively, is essential for the stability of the complexes, but do not influence the reactivity, and consequently the yields of products. Studies toward the structural elucidation of these complexes are underway in our laboratories.

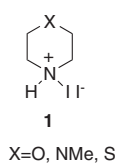


Figure 2. Structure of **1a**, **1b** and **1c**

Table 1. Synthesis of the iodophenols using the complexes **1a-d**

Entry	ArOH	Complex*	Product	Yield / %
1	2	1a	11 **	87
2	2	1b	11	90
3	2	1c	11	80
4	2	1d	11	80
5	4a	1a	13a	92
6	4a	1b	13a	70
7	4a	1c	13a	77
8	4b	1a	13b	70
9	4b	1b	13b	70
10	4c	1a	13c	95
11	4c	1b	13c	90
12	4c	1c	13c	96
13	4c	1d	13c	80
14	4d	1a	13d	70
15	4d	1b	13d	78
16	4d	1c	13d	65
17	5a	1a	SM	-
18	5b	1a	14b	90
19	5b	1b	14b	87
20	5c	1a	14c	70
21	5c	1b	14c	87
22	5d	1a	mixture	-
23	5e	1a	mixture	-
24	3	1a	12	63
25	3	1b	12	60

*1.2 equiv. of complexes **1a**, **1b**, **1c** or **1d** was used. ** ref. 39

In conclusion, in this paper we report the synthesis of new stable in easy to handle amine-iodine complexes **1b** and **1c** from of *N*-methyl-piperazine (**7**) and thiomorpholine (**8**), respectively. These complexes were evaluated for the first time as iodinating reagents of phenols, leading to iodinated products in similar yields to those observed for complex **1a**. The soft conditions used make them useful iodinating agents.

Experimental

General

Melting points were measured with a Fisher-Johns (Fisher Scientific Co) apparatus. ¹H NMR was recorded on a Varian Gemini-200 instrument.

Synthesis of complexes (**1b**, **1c** and **1d**)

Typical procedure for 1b: To a stirred solution *N*-methyl-piperazine **7** (1.0 g, 10 mmol) in 8.0 mL of water

was added dropwise a solution of a mixture of I₂ (2.54 g, 10 mmol) and 4.7 g of the KI in 5.0 mL of water. Orange-red crystals of *N*-methyl-piperazine iodide (**1b**) immediately start to precipitate. The solid was filtered off and washed with cold H₂O. The product was dried under vacuum to provide the desired complex **1b** (3.54 g, 100%).

For complex **1c**: to thiomorpholine **8** (1.03 g, 10 mmol); **1c** (2.85 g, 80%).

For complex **1d**: to *N,N*-tetramethylethylenediamine **9** (1.16g; 10 mmol); **1d** (2.70 g, 75%).

Synthesis of the compounds 11-14

Typical procedure for 13c: To a mixture of methyl 4-hydroxybenzoate **4c** (4.56 g, 30 mmol) and K₂CO₃ (12.6 g, 90 mmol) in an erlenmeyer flask was added distilled water (300 mL). The dark red solution was stirred at room temperature while the complex **1a** or **1b** or **1c** or **1d** (37.5 mmol) or was added in small portions every 15 min during 2 h. The mixture 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 (24 h) and a bright yellow precipitate was formed. The solid was filtered off and washed with cold H₂O. The product was dried under vacuum to provide the desired methyl-3-iodo-4-hydroxybenzoate product **13c** (7.92 g, 95%), or (7.50 g, 90%) or (7.96 g, 96%) or (6.67 g, 80%), respectively. mp 156-158 °C (mp 155-159 °C);⁵⁵ ¹H NMR (200 MHz; CDCl₃) δ 8.37 (1H, d, *J* 2.0 Hz); 7.93 (1H, dd, *J*₁ 8.8 Hz; *J*₂ 2.0 Hz), 7.01 (1H, d, *J* 8.0 Hz), 3.97 (3H, s).

11: mp 178-180 °C (mp 177-179 °C);³⁹ ¹H NMR (200 MHz; CDCl₃) δ 8.14 (1H, dd, *J* 8.0 and 2.0 Hz); 8.08 (1H, dd, *J* 8.0 and 2.0 Hz); 7.78 (1H, td, *J* 8.0 and 2.0 Hz); 7.74 (1H, td, *J* 8.0, 2.0 Hz).

12: mp 90-92 °C (mp 92 °C);⁵⁶ ¹H NMR (200 MHz; CDCl₃) δ 7.93 (1H, d, *J* 9 Hz); 7.73 (overlapping doublets, 2H); 7.54 (1H, t, *J* 8 Hz); 6.90 (1H, d, *J* 8.0 Hz); 7.38 (1H, t, *J* 8.0 Hz); 7.26 (1H, d, *J* 8.0 Hz).

13a: mp 90-92 °C (mp 89-94 °C);¹⁰ ¹H NMR (200 MHz; CDCl₃) δ 7.49 (2H, d, *J* 8.8 Hz); 6.61 (2H, d, *J* 8.8 Hz).

13b: mp 85-87 °C (mp 86-87 °C);⁵⁷ ¹H NMR (200 MHz; CDCl₃) δ 8.60 (1H, d, *J* 2.0 Hz); 8.09 (1H, dd, *J*₁ 7.0 Hz; *J*₂ 2.0 Hz); 7.08 (1H, d, *J* 7.0 Hz).

13d: mp 75-77 °C (mp 78 °C);⁵⁸ ¹H NMR (200 MHz; CDCl₃) δ 7.70 (1H, d, *J* 2 Hz); 7.20 (1H, dd, *J*₁ 8.0 Hz, *J*₂ 2.0 Hz); 6.90 (1H, d, *J* 8 Hz).

14b: mp 180-182 °C (mp 181-182 °C);⁵⁹ ¹H NMR (200 MHz; CDCl₃) δ 9.80 (1H, s); 7.91 (1H, d, *J* 1.8 Hz); 7.46 (1H, d, *J* 1.8 Hz); 3.96 (3H, s).

14c: mp 168-170 °C (mp 169-171.5 °C);²⁴ ¹H NMR (200 MHz; CDCl₃) δ 10.0 (1H, s); 7.55 (1H, d, *J* 8.4 Hz); 6.92 (1H, d, *J* 8.4 Hz); 3.99 (3H, s).

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