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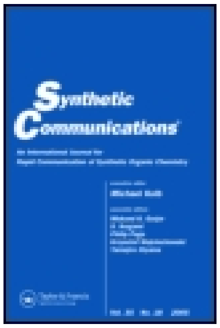

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
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Ultrasound-Promoted Rapid and Efficient Iodination of Aromatic and Heteroaromatic Compounds in the Presence of Iodine and Hydrogen Peroxide in Water

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Accepted author version posted online: 16 Apr 2014.Published online: 16 Apr 2014.

To cite this article: Irlon M. Ferreira , Gleison A. Casagrande , Lucas Pizzuti & Cristiano Raminelli (2014): Ultrasound-Promoted Rapid and Efficient Iodination of Aromatic and Heteroaromatic Compounds in the Presence of Iodine and Hydrogen Peroxide in Water, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, DOI: 10.1080/00397911.2013.879900

To link to this article: http://dx.doi.org/10.1080/00397911.2013.879900

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ULTRASOUND-PROMOTED RAPID AND EFFICIENT IODINATION OF AROMATIC AND HETEROAROMATIC COMPOUNDS IN THE PRESENCE OF IODINE AND HYDROGEN PEROXIDE IN WATER

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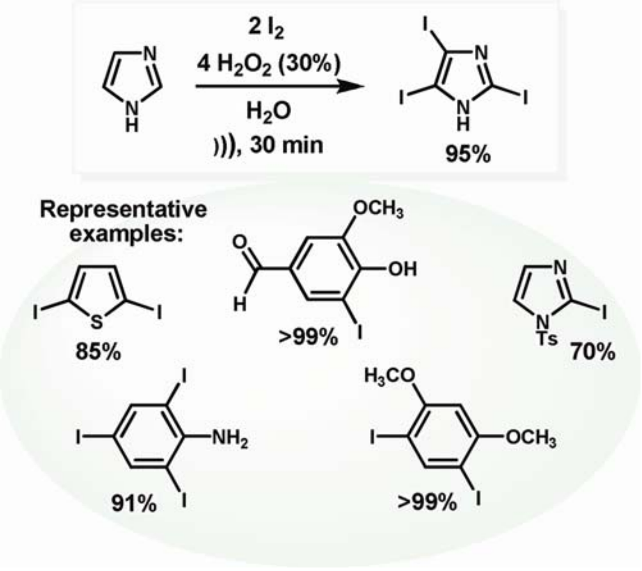
Abstract

A rapid and efficient ultrasound-promoted protocol for iodination of aromatic and heteroaromatic compounds, using molecular iodine in the presence of aqueous hydrogen peroxide in water without any co-solvent, has produced versatile iodinated organic molecules with potential application in organic synthesis and medicine in short reaction times and good to excellent yields.



KEYWORDS: Iodination reaction; ultrasound; reaction in water; mild reaction conditions; iodinated organic compounds

INTRODUCTION

Iodinated organic substrates can be considered versatile building blocks in organic synthesis with application as electrophilic partners in several cross-coupling processes.[1] In addition, iodinated organic compounds have found use in iodine-lithium[1] and iodine-magnesium[2] exchange reactions. The mentioned transformations can be considered import tools in the construction of carbon-carbon and carbon-heteroatom bonds,[1–3] which are employed in total syntheses of complex molecules[4] and in the production of polymers of importance in materials science.[5] Furthermore, a considerable number of iodinated organic compounds are biologically active substances[6] or have found applications in targeted molecular radiotherapy[7] and as contrast media for diagnostic imaging.[8] Consequently, several approaches for iodofunctionalization of organic substances have been developed.[9–12] Among them we can mention protocols for diazotization-iodination[9] and electrophilic iodination using a source of iodine in combination with an oxidizer[10] as important alternatives.

In general, methods involving iodine or iodide and an oxidizer in aqueous media have gained particular attention.[10–12] Accordingly, oxidative iodinations of organic compounds employing molecular iodine and hydrogen peroxide in aqueous media have emerged as practical protocols.[11] In this context, our research group has recently published a communication employing the I_2/H_2O_2 (30%) system in the absence of an acidic catalyst using water without any co-solvent for the preparation of iodinated aromatic and heteroaromatic compounds.[12] Although this transformation and many other oxidative iodofunctionalizations can be considered important methodologies for introducing an iodine atom into an organic molecule, in most cases, they have the drawback of being time-consuming processes.[10–12]

In this sense, the use of ultrasound in organic synthesis has proven to be an important strategy for reducing reaction times and for improving yields.[13] These features of sonochemistry have been explored in the development of environmentally benign synthetic methods.[14] There is a wide literature illustrating the mildness and non-hazardous character of ultrasound and its effectiveness for acceleration of organic reactions,[15] including our contribution to this area.[16]

To the best of our knowledge there is no method for the iodination of aromatic and heteroaromatic compounds employing molecular iodine and hydrogen peroxide in water promoted by ultrasonic irradiation reported in the literature. Having in mind the requirement for iodinated aromatic and heteroaromatic compounds for synthetic purposes, along with the virtual applicability of iodinated compounds in medicine, we focused on development of a methodology which uses molecular iodine as the iodine source of choice, aqueous hydrogen peroxide as a safe and environmentally accepted oxidizer and water as a non-flammable and innocuous solvent, employing ultrasonic irradiation as energy source, in order to produce iodinated aromatic and heteroaromatic compounds with potential application in organic synthesis and medicine in high yields and short reaction times.

RESULTS AND DISCUSSION

Despite the versatility of the protocol previously reported by us for the iodination of aromatic and heteroaromatic compounds using iodine and hydrogen peroxide in water,[12] the method published can be considered rather time-consuming. In order to circumvent such drawback, we decided to apply the ultrasonic irradiation as energy source to reach a faster methodology for the preparation of iodinated aromatic and heteroaromatic compounds. As can be seen in Table 1, entry 1, iodinated compound **2a** was not obtained when the reaction of phenol (**1a**) with 2 equiv of iodine was carried out under ultrasonic irradiation in the absence of hydrogen peroxide (30%) for 360 min. This experiment was performed based on evidences involving the production of hydrogen peroxide by water sonication.[17] When we sonicated phenol (**1a**) with 2 equiv of iodine and 2 equiv of hydrogen peroxide for 60 min, 2,4,6-triiodophenol (**2a**) was obtained in a 43% yield (Table 1, entry 2). In an attempt to improve the yield, we conducted the same transformation using 2 equiv of iodine and 4 equiv of hydrogen peroxide (30%). In this case, the triiodinated phenol **2a** was isolated in a satisfactory yield of 74%. When we allowed substituted phenols **1b-i** to react with 1.5 equiv of iodine and 3 equiv of hydrogen peroxide (30%), the obtained results show that the success of our reaction depends on the electronic effects promoted by the substituent attached to the aromatic ring (entries 4-11). The reaction proceeded smoothly for phenols bearing electron withdrawing substituents such as 4-hydroxyacetophenone (**1b**) (entry 4), 4-nitrophenol

(**1c**) (entry 5) and 4-chlorophenol (**1d**) (entry 6) providing iodinated phenols in excellent yields after sonication for 30-60 min. On the other hand, the treatment of 4-methoxyphenol (**1e**) with iodine and hydrogen peroxide for 360 min under sonication did not lead to the formation of the desired product **2e** (entry 7). In this reaction the starting material was completely consumed and a mixture of hydroquinone and unidentified substances was produced. Besides, the reaction of *p*-cresol (**1f**) under sonication for 60 min furnished 2,6-diido-4-methylphenol (**2f**) in a poor 40% yield (entry 8) along with unidentified materials. By using 2-bromophenol (**1g**), which is blocked at the 2-position with an electron withdrawing substituent, we obtained 2-bromo-4,6-diiodophenol (**2g**) in a 96% yield after ultrasonic irradiation for 60 min (entry 9). Accordingly, sonication of 2,6-dichlorophenol (**1h**) and iodine in the presence of hydrogen peroxide for 45 min, gave 2,6-dichloro-4-iodophenol (**2h**) in a 97% yield (entry 10). In the same direction, allowing 4-hydroxy-3-methoxybenzaldehyde (**1i**) to react with 1.5 equiv of iodine and 3 equiv of hydrogen peroxide under ultrasonic irradiation for only 30 min, we obtained 4-hydroxy-3-iodo-5-methoxybenzaldehyde (**2i**) in a quantitative yield (entry 11). In order to examine the scope and limitations of our methodology beyond phenol derivatives, we carried out the reaction of aniline (**1j**) with 2 equiv of iodine and 4 equiv of hydrogen peroxide (30%) using water as solvent under ultrasonic irradiation. After 60 min, we obtained 2,4,6-triiodoaniline (**2j**) in a 91% yield (entry 12). As can be seen in Table 1, entry 13, 2-bromo-1,3,5-triiodobenzene (**2k**) was not obtained even after 360 min of sonication and the starting material **1k** was recovered. This experiment shows that the success of our reaction depends dramatically on the electronic effects promoted by the substituent attached to the aromatic ring. When we subjected *N*-Boc-aniline (**1l**) to the sonication with 2 equiv of iodine and 4 equiv of hydrogen peroxide (30%) in water for 75 min, 4-iodo-*N*-Boc-aniline (**2l**) was isolated in a 91% yield (entry 14). This experiment shows that our reaction is rather sensible to the steric effect exerted by the substituent bonded to the aromatic ring. In agreement with this finding, when we allowed anisole (**1m**) to react with 2 equiv of iodine and 4 equiv of hydrogen peroxide (30%) (entry 15), we did not observe the formation of *ortho*-iodinated anisoles. Under the mentioned conditions, we obtained the monoiodinated anisole **2m** in a quantitative yield after sonication of 90 min. Afterwards, we allowed the reaction of the electron-rich 1,3-dimethoxybenzene (**1n**) with 1 equiv of iodine and 2 equiv of hydrogen peroxide (30%) for 45 min and obtained 1,5-diiodo-2,4-dimethoxybenzene (**2n**) in a quantitative yield (entry 16). Ultimately, for producing iodinated heteroaromatic compounds, we carried out the transformation employing imidazole (**1o**), 2 equiv of iodine and 4 equiv of hydrogen peroxide (30%). In this reaction, triiodoimidazole (**2o**) was produced in an excellent yield of 95% in only 30 minutes of sonication (entry 17). On the other hand, when 1-tosylimidazole (**1p**) was treated with 2 equiv of iodine and 4 equiv of hydrogen peroxide (30%) in water, 2-iodo-1-tosylimidazole was produced in a 70% yield (**2p**) after sonication for 90 min (entry 18). By performing the reaction between thiophene (**1q**) and 2 equiv of iodine and 4 equiv of hydrogen peroxide (30%) in water under sonication for 75 min, 2,5-diiodothiophene (**2q**) was produced in an 85% yield (entry 19).

The structures of compounds **2a-q** have been assigned on the basis of a variety of spectroscopic techniques, namely, accordingly to their IR, MS, ^{1}H and ^{13}C NMR spectra. All substances produced (**2a-q**) were previously synthesized by other synthetic methodologies and provided melting point values and spectral data which are in agreement with those already published.

CONCLUSIONS

In summary, a rapid and efficient ultrasound-promoted reaction for the preparation of iodinated aromatic and heteroaromatic compounds has been developed and versatile organic molecules with potential application in organic synthesis and medicine were produced in very good yields, under mild and safe reaction conditions, which include molecular iodine, hydrogen peroxide (30%) and water as solvent.

EXPERIMENTAL

General Methods

Reactions were carried out with a Microtip Probe connected to a Sonics Vibra-cell Ultrasonic Processor (500 W) operating at 20 KHz (100 W). ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) and on a Bruker DRX 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometers in $CDCl_3$, DMSO-d_6 or CD_3OD solutions using TMS as internal standard. Mass spectra were produced at 70 eV using a Shimadzu MS-QP5050A mass spectrometer connected to a Shimadzu GC-17A gas chromatograph or a Varian MS-210 mass spectrometer connected to a Varian GC-431 gas chromatograph. Infrared spectra were recorded on a Bomem MB-100 FT-IR spectrometer using KBr pellets in the 4000-400 cm^{-1} region. Uncorrected melting point values were recorded on an Instrutherm DF-3600 apparatus.

General Procedure For Ultrasound-Promoted Iodination Of Aromatic And Heteroaromatic Compounds

To a suspension of the appropriate aromatic or heteroaromatic compound (**1a-q**) (2 mmol) and molecular iodine (2-4 mmol) in distilled water (10 mL) was added hydrogen peroxide 30% (m/v) (4-8 mmol). The mixture was sonicated and the progress of reaction was monitored by TLC. Afterwards, a saturated sodium thiosulfate aqueous solution (10 mL) was added to the mixture, which was extracted with ethyl acetate (3 × 20 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an appropriate eluent, affording the desired product (**2a-q**).

Full experimental details and characterization data of products are available in the Supplementary Content.

Characterization Data For 2,4,6-Triiodophenol (2a) (CAS Number: 609-23-4)

Yield: 0.6980 g (74%); yellowish solid; mp 153-154°C (hexane as eluent) (lit.[18] 152-153°C); IR (KBr, cm^{-1}): 3439, 3053, 1434, 1369, 1136, 533; ^{1}H NMR 500 MHz ($CDCl_3$, ppm): 7.93 (s, 2H), 5.77 (s, 1H); ^{13}C NMR 125 MHz ($CDCl_3$, ppm): 153.7, 146.4, 83.3, 83.2; EI-MS (*m/z*, %): 472 (100.0), 218 (8.3), 127 (7.3).

ACKNOWLEDGMENTS

We gratefully acknowledge the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), the Fundação de Amparo à Pesquisa do Estado de São Paulo

(FAPESP) and the Fundação de Apoio ao Desenvolvimento do Ensino, Ciência e Tecnologia do Estado de Mato Grosso do Sul (FUNDECT) for financial support.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website. Please make the words "publisher's website" a live DOI link.

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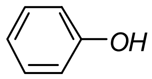
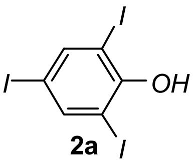
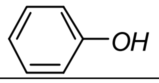
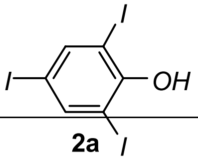
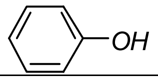
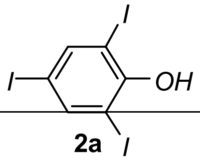
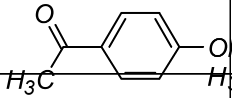
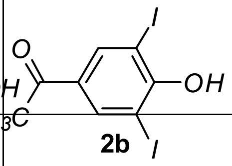
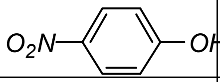
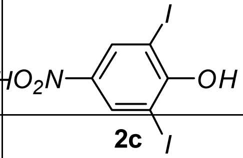
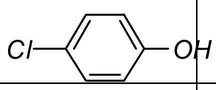
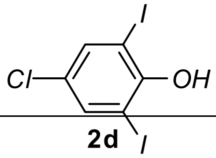
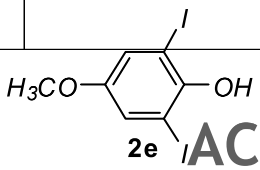
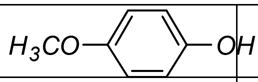
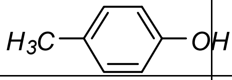
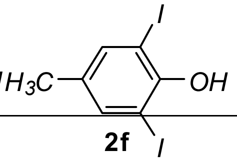
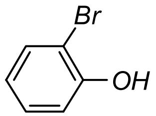
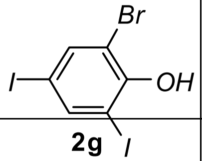
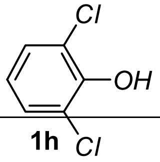
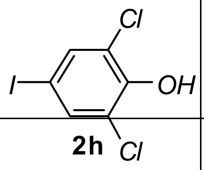
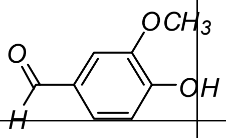
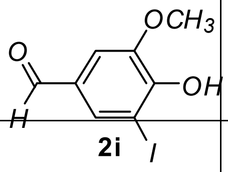
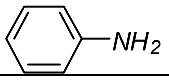
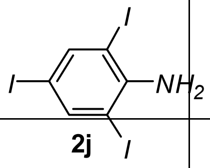
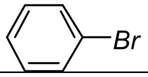
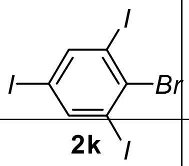
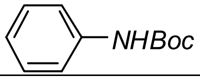
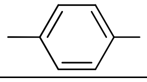
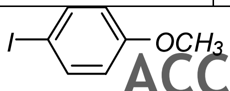
Table 1. Synthesis of iodinated aromatic and heteroaromatic compounds (**2**) by the reaction of aromatic and heteroaromatic compounds (**1**) with iodine and hydrogen peroxide in water under ultrasonic irradiation.[a]

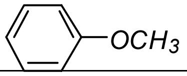
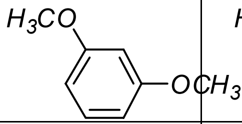
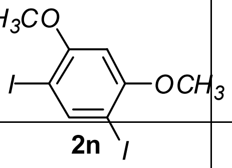
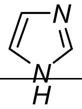
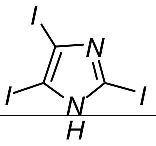
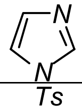
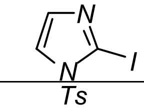
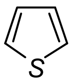
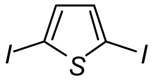
Entry	Aromatic compound (**1**)	Iodinated compound (**2**)	I_2 / H_2O_2 equivalents	Time (min)	Isolated yield (%)
1	 **1a**	 **2a**	2 / 0	360	0
2	 **1a**	 **2a**	2 / 2	60	43
3	 **1a**	 **2a**	2 / 4	60	74
4	 **1b**	 **2b**	1.5 / 3	45	97
5	 **1c**	 **2c**	1.5 / 3	45	88
6	 **1d**	 **2d**	1.5 / 3	45	90


2e

7	 **1e**		1.5 / 3	360	0
8	 **1f**	 **2f**	1.5 / 3	60	40
9	 **1g**	 **2g**	1.5 / 3	60	96
10	 **1h**	 **2h**	1.5 / 3	45	97
11	 **1i**	 **2i**	1.5 / 3	30	>99%
12	 **1j**	 **2j**	2 / 4	60	91
13	 **2k**	 **2k**	2 / 4	360	0
14	 **1l**	 **2l**	2 / 4	75	91



2m

15	 **1m**		2 / 4	90	>99%
16	 **1n**	 **2n**	1 / 2	45	>99%
17	 **1o**	 **2o**	2 / 4	30	95
18	 **1p**	 **2p**	2 / 4	90	70
19	 **1q**	 **2q**	2 / 4	75	85

[a]Reaction conditions: 2 mmol of compound **1**, the indicated amount of I_2, the indicated amount of H_2O_2 (30%) and 10 mL of H_2O were maintained under sonication (20 KHz e 100 W) for the period of time presented.