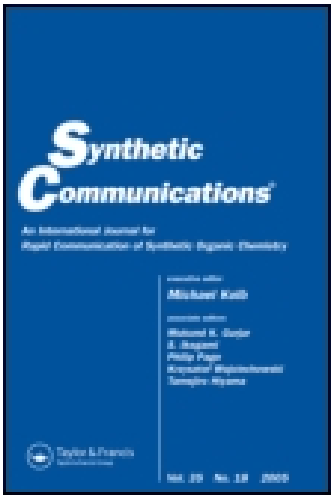

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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Highly Efficient Method for Synthesis of Benzoquinones Using Hypervalent Iodine(III) Reagent and Sodium Bisulfate

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Published online: 27 Dec 2013.

To cite this article: Kulbhushan A. Sasane & Vikas N. Telvekar (2014) Highly Efficient Method for Synthesis of Benzoquinones Using Hypervalent Iodine(III) Reagent and Sodium Bisulfate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:4, 468-473, DOI: 10.1080/00397911.2013.804930

To link to this article: http://dx.doi.org/10.1080/00397911.2013.804930

Synthetic Communications®, 44: 468–473, 2014

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.804930

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HIGHLY EFFICIENT METHOD FOR SYNTHESIS OF BENZOQUINONES USING HYPERVALENT IODINE(III) REAGENT AND SODIUM BISULFATE

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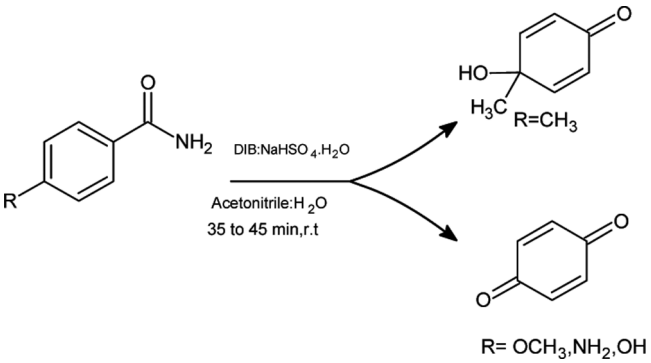
GRAPHICAL ABSTRACT



Abstract *A rapid, one-step, novel approach for the conversion of benzamides into benzoquinones using (diacetoxyiodo)benzene(III) and sodium bisulfate has been developed in aqueous acetonitrile at room temperature. The developed protocol is applicable to several types of substituted benzamide derivatives to get the corresponding benzoquinone products. The developed methodology offers mild reaction condition, short reaction time, and moderate to excellent yields. This is one of the most simple and environmentally benign protocols for synthesis of benzamide derivatives.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Benzamides; benzoquinones; hypervalent iodine; sodium bisulfate

INTRODUCTION

Quinones are large class of compounds having rich and interesting chemistry. Natural products having benzoquinone structures show biologically significant properties such as cardiovascular, antitumor, antibacterial, antigerminative, and

Received January 9, 2013.
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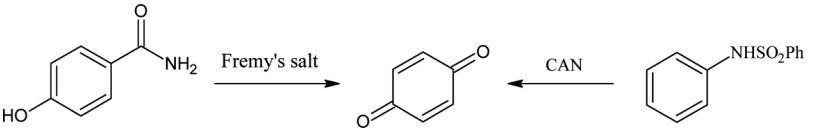


Scheme 1. Some methods for synthesis of benzoquinones.

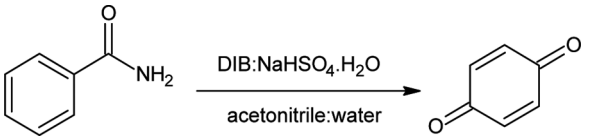
antiprotozoan activities. Large numbers of chemical derivatives with 1,4-benzoquinone as the basic subunit exhibit prominent pharmaceutical applications such as antibiotic,[1] antitumor,[2] antimalarial,[3] antineoplastic,[4] anticoagulant,[5] and herbicidal activities.[6]

In general, quinones are being synthesized by oxidation of phenols, 1,4-dihydroxybenzenes or hydroquinones, and dimethybenzenes using ceric ammonium nitrate (CAN),[7] 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[8] nitric acid,[9] salcomine/O_2,[10] chromium oxidants,[11] benzene selenic anhydride,[12] silver oxide,[13] manganese oxide,[14] and $NaBrO_3$ / wetK_{10}[15] as oxidizing agents. There are two reports of the oxidative degradation of *p*-hydroxybenzamide using Fremy's salt, whereas in another method iodobenzene in combination with oxone was used for synthesis of 1,4-benzoquinone by Hofmann rearrangement from benzamide.[16,17] These two conversions required longer reaction times and had lower substrate compatibility, which limit their applications (Scheme 1).

Therefore, there is need to develop dynamic and feasible protocols for the transformation of benzamide to benzoquinone, which can activate under milder reaction conditions. Considering these issues, we focused our attention toward the expansion of a novel protocol for the synthesis of quinone derivatives.

RESULTS AND DISCUSSION

Our research group is mainly working on the hypervalent iodine reagents. During our study we found that (diacetoxyiodo)benzene(III), which is readily available and frequently used in several oxidative transformations, can be used for the synthesis of quinones from benzamides. Thus for our initial studies, we used benzamide as a starting material. It was observed that when benzamide oxidized using (diacetoxyiodo)benzene, a lower yield (15%) of quinone was isolated after long reaction time in water–acetonitrile (1:1) as a solvent. It was found that during the reaction many other unidentified by-products were also formed. Further screening of reagent and reaction conditions revealed that (diacetoxyiodo)benzene in the presence of sodium bisulfate leads to formation of a single product with good yield within short reaction time (Scheme 2).



Scheme 2. Benzamide to benzoquinone using (diacetoxyiodo) benzene and sodium bisulfate.

Table 1. Optimization of reagent conditions[a]

Entry	DIB (mmol)	$NaHSO_4$ (mmol)	Time (min)	Yield (%)
1	1	1	45	45
2	3	1	45	67
3	5	1	45	85
4	5	1	60	83
5	5	2	45	85
5	6	2	45	82

[a]Reaction conditions: Benzamide (1 mmol) in water–acetonitrile (1:1) as solvent at room temperature.

It was reported in the literature that the treatment of (diacetoxyiodo)benzene with sodium bisulfate leads to the formation of reactive hydroxy (phenyl) iodonium ions,[18]and we thought that reactive hydroxy(phenyl) iodonium ions may accelerate the formation of quinone from benzamide. Further investigation of reaction found that 5 equivalents of (diacetoxyiodo)benzene and 1 equivalent of sodium bisulfate is suitable for conversion of 1 equivalent of benzamide to quinone (Table 1).

Under these reaction conditions various solvent systems were tried, and it was found that water–acetone–dichloromethane are suitable solvents, but lower yields were obtained as compaired to the water–acetonitrile (1:1) solvent system.

To study the prospective and general applicability of the developed methodology, various benzamides containing different functional groups were investigated, and results are summarized in Table 2. It was observed that 2-methyl benzamide and 2-chlorobenzamide reacted smoothly to obtained good yield of respective benzoquinone derivatives (Table 2, entries 2–4).It is remarkable to mention that in case of *para* substituted methoxy, the deprotection followed by oxidation was observed (Table 2, entry 6), whereas in the case of *meta*-substituted methoxy no deprotection was observed (Table 2, entry 5). Similarly *para*-substituted hydroxy and amino benzamide converted into benzoquinone (Table 2, entries 7 and 8).

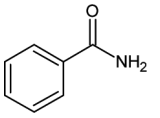
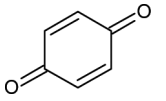
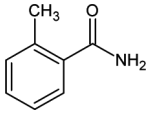
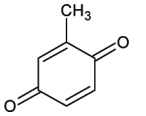
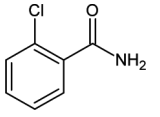
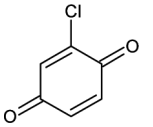
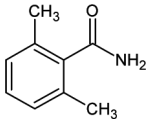
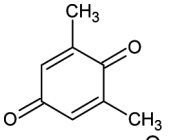
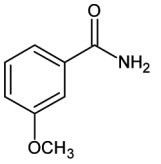
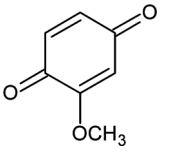
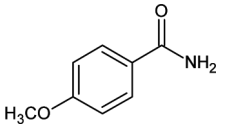
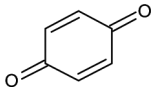
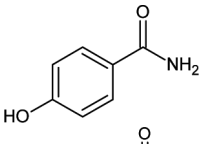
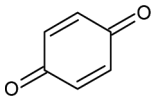
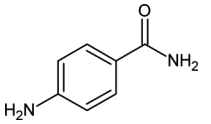
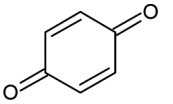
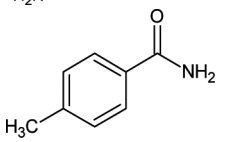
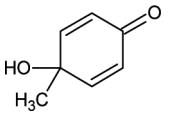
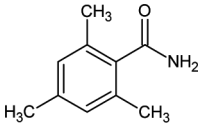
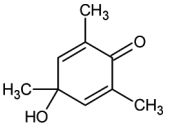
It was observed that *para*-methyl benzamide and 2,5-dimethyl benzamide gives substituted products instead of quinone (Table 2, entries 9 and 10). Reaction of aliphatic amides does not take place with this reaction system (Table 2, entry 11).

In summary, we developed a new application of (diacetoxyiodo)benzene(III) and sodium bisulfate system in aqueous acetonitrile for synthesis of benzoquinones from corresponding benzamides. The advantages of the present method are use of simple shelf reagents, mild reaction conditions, and good yields.

General Procedure for Synthesis of Benzoquinone Derivatives (Table 2, Entry 1)

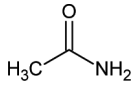
(Diacetoxyiodo) benzene (5 mmol, 1.61 g) and $NaHSO_4 \cdot H_2O$ (1 mmol, 0.138 g) were stirred for 10–15 min at room temperature in aqueous solution of acetonitrile (5 ml water and 5 ml acetonitrile). In this reaction mixture benzamide (1 mmol) was added and stirring was continuing until reaction went to completion, as monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was quenched with water and further extracted with chloroform

Table 2. Reaction of amides using (diacetoxyiodo) benzene and sodium sulfate[a]

Entry	Substrate	Product[b]	Time (min)	Yield (%)[c]
1			30	80
2			35	85
3			40	78
4			40	85
5			40	72
6			40	75
7			45	70
8			45	71
9			45	70
10			45	78

(*Continued*)

Table 2. Continued

Entry	Substrate	Product[b]	Time (min)	Yield (%)[c]
11		—	24 hrs	No reaction

[a]Reaction conditions: amides (1 mmol), (diacetoxyiodo)benzene (5 mmol), sodium bisulfate (1 mmol) in aqueous acetonitrile (10 mL) at room temperature.
[b]Products were characterized using ^{1}H NMR, IR, and mp/bp and compared with literature data.
[c]Isolated yields of pure products.

(3×10 ml). The combined chloroform layers were washed with water (3×20 ml), dried over Na_2SO_4, and concentrated on a rota-evaporator to get the crude residue. The residue was further purified by column chromatography on silica gel using ethyl aceate–hexane (1:9) as an eluent to afford pure benzoquinone.

1,4-Benzoquinone (Table 2, Entry 1)

Mp 115 °C (lit.[19] mp 112 °C); ^{1}H NMR (60 MHz, $CDCl_3$): 7.59–7.68 (s, 4H); IR (KBr, cm^{-1}): 3165, 3070, 1665, 1589, 1312, 1264, 897.

SUPPORTING INFORMATION

Full experimental detail, ^{1}H NMR, IR and MP/BP can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENT

K. A. S. is thankful to the Council of Scientific and Industrial Research (New Delhi) for the award of a Senior research fellowhip and financial support.

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