A New Combination of Cyclohexylhydrazine and IBX for Oxidative Generation of Cyclohexyl Free Radical and Related Synthesis of Parvaquone

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Graphical Abstract

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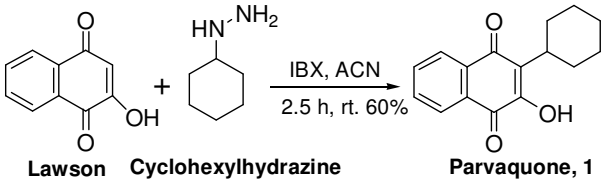

Lawson **Cyclohexylhydrazine** **Parvaquone, 1**

- Novel, simple and mild transformation
- Satisfactory yield of 60% in single step
- Free from transition metals and hazardous peroxides

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A New Combination of Cyclohexylhydrazine and IBX for Oxidative Generation of Cyclohexyl Free Radical and Related Synthesis of Parvaquone

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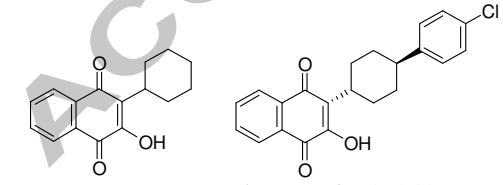
ABSTRACT

The present paper demonstrate a single-step and straightforward synthesis of parvaquone through intermediacy of cyclohexyl radical generated from novel combination of cyclohexylhydrazine and *o*-iodoxybenzoic acid and subsequently trapped by 2-hydroxy-1,4-naphthoquinone. Formation of cyclohexyl free radical using this new combination was reaffirmed by cyclohexylation of readily available 2-amino-1, 4-naphthoquinone.

Quinones, including 1,4-benzoquinones and 1,4-naphthoquinones are ubiquitous in nature and essentially contributed into wide range of pharmaceutical and natural products.[1] Specifically, hydroxylated naphthoquinones are precisely known to have remarkable biological activities such as antifungal, anti-inflammatory, antiallergic, antiplatelet, antibacterial, antibiotic and apoptosis.[2] Hydroxylated naphthoquinones bearing alicyclic rings at 2 or 3 positions are widely used for suppression of trophozoites in ducks, chickens and monkeys infected with blood induced malaria.[3] For example, 2-cyclohexyl-3-hydroxy-1,4-naphthoquinone (parvaquone (marketed as Clexon), **1**) and *trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione (atovaquone, **2**) are leading members of this class due to their clinically useful antiprotozoal activities.[4-8] (Fig. 1).

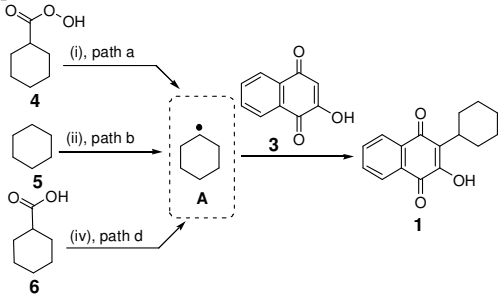


Parvaquone, 1 (antiprotozoal) **Atovaquone, 2** (antimalarial)

Fig. 1. Clinically used alicyclic hydroxylated naphthoquinone drugs.

Atovaquone **2** has been used for *Pneumocystis carinii* pneumonia (PCP), a parasitic lung infection of immunocompromised patients.[5] Additionally, it has been also used in the treatment of malaria,[6] toxoplasmosis[7] and babesiosis.[8] On the other hand, parvaquone is gaining remarkable importance towards controlling a devastating cattle disease, *Theileriosis* (*East Coast Fever*) in central and eastern African countries which is caused due to parasite *Theileria parva.*[9] According to the study done, there is annual loss of 1.1 million cattle and more than 250 million are at risk due to lack of effective treatment of *Theileriosis.*[9a]

These cyclohexylated naphthoquinone drugs are predominantly synthesized through trapping of corresponding cyclohexyl free radicals by related naphthoquinones counterparts.[10-11] Parvaquone **1** was synthesized through generation of cyclohexyl free radical **A** in the presence of 2-hydroxy-1, 4-naphthoquinone **3** by using various approaches (Scheme 1).[3, 10] First report on cyclohexyl radical mediated synthesis of parvaquone was disclosed by Fieser and Leffler while generating cyclohexyl free radical thermally from cyclohexanecarboperoxoic acid **4** in the presence of lawson **3** to afford **1** in 45% yield[3] (Scheme 1, path a). Later on, Amini and Huyser demonstrated synthesis of **1** in 53% yield through generating cyclohexyl free radical from cyclohexane **5** by using *tert*-butyl peroxide as radical initiator in the process[10a](Scheme 1, path b).



Reagents and conditions: (i) HOAc, 100 °C, 45%. (ii) $(CH_3)_3COOC(CH_3)_3$, 125 °C, 53%. (iii) $Cu(OTf)_2$, TBHP, 80 °C, 6 h, 72%. (iv) $AgNO_3/(NH_4)_2S_2O_8$, ACN/H_2O, 65-70 °C, 25%.

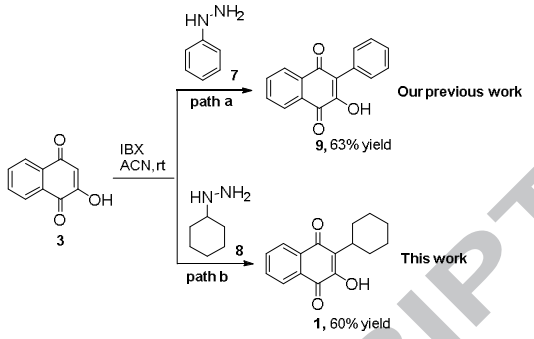
Scheme 1. Various approaches for cyclohexyl radical mediated synthesis of parvaquone **1**.

Recently, Lee and coworkers also described synthesis of **1** through generation of cyclohexyl radical from cyclohexane in presences of *tert*-butyl hydroperoxide and copper (II) triflate at 80 ^{0}C provided **1** in 72% yield after 6 h [10b] (Scheme 1, path c). Khambay and Batty contributed by demonstrating new method through generating cyclohexyl free radical from cyclohexanecarboxylic acid **6** using a combination of silver nitrate/ammonium persulfate to provide **1** in 25% yield[10c] (Scheme 1, path d).

Aforementioned synthetic methods retain their disadvantages of affording low yields due to formation of by-product,[10c] requirement of high temperature,[3, 10a] uses of hazardous peroxides[10a] and expensive catalyst such as $AgNO_3$.[10c] Besides free radical based methods, there are few reports available for the synthesis of **1**[12a] and its derivatives[12b]comprising multistep approaches. Use of Grignard reagents, cryogenic reaction conditions and requirement of special handling for reagents restricted these processes from being generalized.[12] A step forward towards overcoming these problems was our latest development of transition metals free, simple and efficient four steps process by using cheaply and commercially available raw materials such as 1-naphthol and cyclohexanol under mild conditions.[13]

Recently, we have disclosed novel combination of arylhydrazine and IBX for oxidative generation of aryl free radical and subsequently trapping by differently substituted naphthoquinones[14] and anilines[15] resulting in new methods for C- and N-arylations, respectively. On the same lines as IBX mediated oxidative free radical arylation of naphthoquinones (Scheme 2, path a) and considering the potential of **3** to trap cyclohexyl free radical (Scheme 1, path a-d), we envisaged that if cyclohexyl free radical gets formed by combination of cyclohexylhydrazine **8** and IBX, it would be trapped by **3** ultimately leading to a novel route for synthesis of parvaquone **1** (Scheme 2, path b). To attest this hypothesis we choose **3** and **8** as starting materials. Requirement of **8** was fulfilled by synthesizing it using literature procedure. [16]

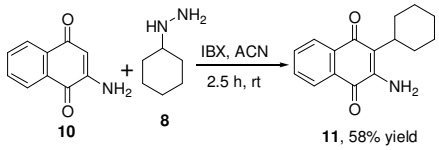
When to a mixture of **3** and IBX in acetonitrile was added dropwise **8** at room temperature, immediately evolution of nitrogen gas in the form of bubbles was observed. We inferred that the formation of nitrogen gas during the course of reaction might be due to oxidation of **8** by IBX.



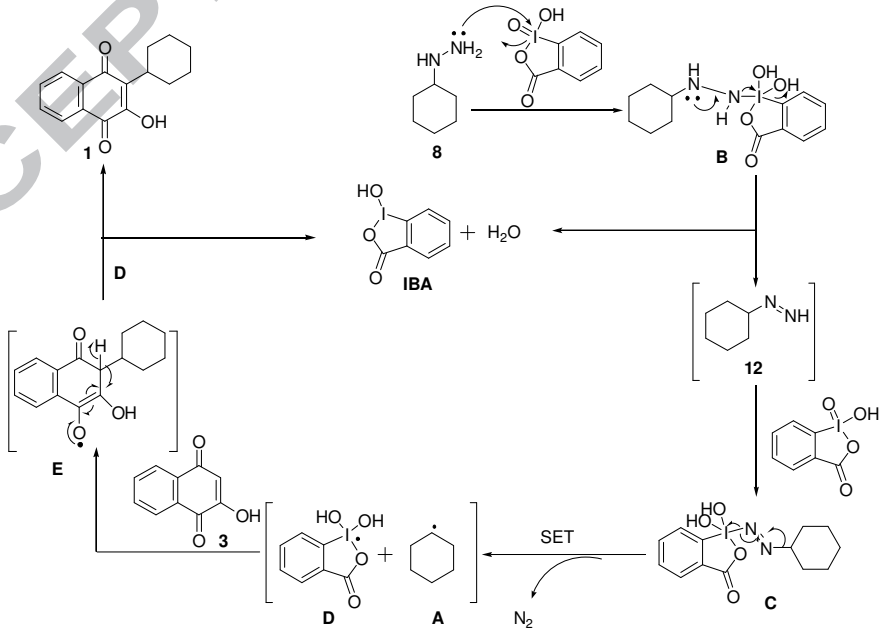
Scheme 2. IBX mediated oxidative arylation and cyclohexylation of **3**.

After completion of reaction, crude product was isolated and purified by using column chromatography. Spectral characterization data of the isolated pure product confirmed the formation of parvaquone, **1** in satisfactory yield of 60% (Scheme 2, path b).

To reaffirm the formation of cyclohexyl free radical using this new combination of cyclohexylhydrazine **8** and IBX, cyclohexylation of readily available 2-amino-1, 4-naphthoquinone **10** was attempted. Thus when the reaction was performed using **10** as substrate under the same reaction conditions expected product 2-amino-3-cyclohexyl-1, 4-naphthoquinone, **11** was isolated in satisfactory yield of 58% (Scheme 3).



Scheme 3. IBX mediated synthesis of 2-amino-3-cyclohexyl-1, 4-naphthoquinone, **11**.



Scheme 4: Cyclohexyl radical mediated postulated mechanism for formation of **1**.

In our previous studies on arylation of naphthoquinones it has been proved, through radical trapping experiments, that the combination of arylhydrazine and IBX generates aryl free radicals.[14-15] On the same lines we postulate cyclohexyl free radical mediated mechanism for the reaction leading to formation of **1** (Scheme 4). Attack of cyclohexylhydrazine on electrophilic iodine of IBX would form intermediate **B** which on redox decomposition may form cyclohexyldiazine **12** and *o*-iodosobenzoic acid (IBA). Further highly nucleophilic **12** would attack on another molecule of IBX forming an intermediate **C**. Intermediate **C** on oxidative extrusion of nitrogen would leave behind two free radical species **A** and **D** by single electron transfer mechanism demonstrated by Nicolaou et al.[17] Cyclohexyl free radical **A** would then attack on unsubstituted electrophilic position of corresponding quinoid ring of **3** to form **1** after removal of water molecule presumed through interaction of free radical intermediates **E** and **D**. Observance of evolution of nitrogen gas during the course of reaction and recovery of IBA as a by-product are found supportive toward the postulated radical mediated mechanism.

In conclusion, we have established a novel protocol for generation of cyclohexyl free radical alongside a new, mild, and single step method for synthesis of parvaquone. This new method could be considered as competent alternative to the previously reported free radical based methods as it circumvent toxic transition metals, hazardous peroxides, high temperature and longer reaction time. We believe that the developed method could be considered as valuable entry not only for parvaquone but also toward exploration of synthesis of other similar molecules through combination of appropriate hydrazines and IBX. A free radical mediated mechanism is postulated for the reaction based on observations and previously established IBX chemistry.

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Supplementary Material: ^{1}H NMR for compound **1** and ^{1}H, ^{13}C NMR spectra for compound **11** are can be found, in the online version at http://dx.doi.org/j.tetlet.

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Experimental

General Methods: Commercial grade solvents and reagents were used without further purification. Silica gel-G plates (Merck) were used for TLC analysis. Column chromatography was carried out using silica gel 60 (70-230 mesh. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded with Bruker 300 MHz and 400 MHz instrument using $CDCl_3$ as a solvent and TMS as internal standard. Infrared spectra were recorded with a Perkin-Elmer spectrum 100 instrument.

Typical procedure and characterization data for compound 1 and 10:

Synthesis of 2-cyclohexyl-3-hydroxy-1,4-naphthoquinone (parvaquone) (1): To a solution of **3** (1.0 g, 5.74 mmol) in acetonitrile (20 mL) was added IBX (3.80 g, 13.6 mmol) in one lot and stirred for 5 min at room temperature. To this was added dropwise a solution of **8** (0.78 g, 6.8 mmol) dissolved in 10 mL of acetonitrile over the course of 20 min. During the addition of **8** exotherm (up to 35 °C) was observed with evolution of nitrogen gas in the form of bubbles. Reaction progress was monitored by TLC (using mobile phase, hexane: ethyl acetate/5:95). After satisfactory TLC, water (20 mL) was added to the reaction mixture and acetonitrile was evaporated using rotary evaporator. To the residue obtained was added dichloromethane (30 mL). Oganic layer was separated and washed with saturated sodium bicarbonate solution followed by saturated solution of sodium sulphite. Separated organic layer was dried over anhydrous sodium sulphate and evaporated to obtain crude **1** which was further purified by column chromatography (mobile phase - hexane: ethyl acetate/5:95) to afford **1** as yellow solid, (0.88 g, 60% yield); mp 136-138 °C (lit.[18] 135-136°C); FT-IR (KBr): 3585, 3513, 3071, 2926, 2853, 1666, 1604, 1590 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-7.96 (m, 2H), 7.82-7.59 (m, 2H), 7.34 (s, 1H, OH), 3.22-2.85 (m, 1H), 1.85-1.12 (m, 10H) ppm; ^{13}C NMR (75 MHz; $CDCl_3$): δ 184.5, 181.9, 152.8, 135.1, 134.9, 132.7, 129.2, 127.9, 126.9, 125.9, 35.1, 29.2, 26.7, 25.9.

Synthesis of 2-amino-3-cyclohexyl-1,4-naphthoquinone (11): Above mentioned procedure for synthesis of **1** was similarly followed for synthesis of **11** by using **10** (1.0 g, 5.77 mmol), IBX (3.87 g, 13.8 mmol) and cyclohexylhydrazine (0.79 g, 6.92 mmol) to provide **11** as orange red solid, (0.85 g, 58% yield); mp 125-128 °C; FT-IR (KBr): 3466, 3372, 3071, 2926, 2853, 1666, 1604, 1575, 1446, 1384 and 1282 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.05-7.98 (dd, *J* = 21 Hz, 2H), 7.67-7.58 (dd, *J* = 27 Hz, 2H), 5.24 (s, broad, 2H), 2.78 (m, 1H), 1.93-1.34 (m, 10H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 182.6, 181.8, 144.3, 134.0, 133.2, 131.6, 129.9, 126.0, 125.3, 120.4, 36.4, 29.0, 26.8, 25.8; Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.33; H, 6.68; N, 5.45; Found: C, 75.29; H, 6.66; N, 5.49.

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Highlights

- New method of generating cyclohexyl radical by using IBX and cyclohexylhydrazine.
- Parvaquone synthesized in 60% yield using metal, hazardous peroxide free conditions.
- Described method has advantages of single step and mild reaction conditions.
- The mechanism for cyclohexyl radical mediated synthesis of parvaquone is postulated.