RSC Advances

ROYAL SOCIETY OF CHEMISTRY

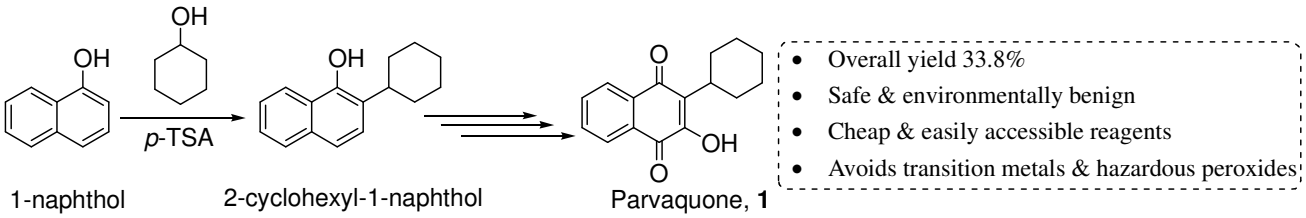
www.rsc.org/advances

Table of Graphics

Simple and Effective Route for Synthesis of Parvaquone, an Antiprotozoal Drug

Pravin C. Patil and Krishnacharya G. Akamanchi*

Parvaquone, an antiprotozoal agent against *Theileria parva*, was synthesized in 33.8% overall yield by using cheap and commercial raw materials. Key intermediate, 2-cyclohexyl-1-naphthol was synthesized in 86% yield by cyclohexylation of 1-naphthol and further converted into parvaquone in good yield through reaction sequences such as oxidation, epoxidation followed by isomerization.



Journal Name

RSCPublishing

COMMUNICATION

Simple and Effective Route for Synthesis of Parvaquone, an Antiprotozoal Drug

Cite this: DOI: 10.1039/x0xx00000x

Pravin C. Patil[a] and Krishnacharya G. Akamanchi*

Received
Accepted

DOI: 10.1039/x0xx00000x

www.rsc.org/

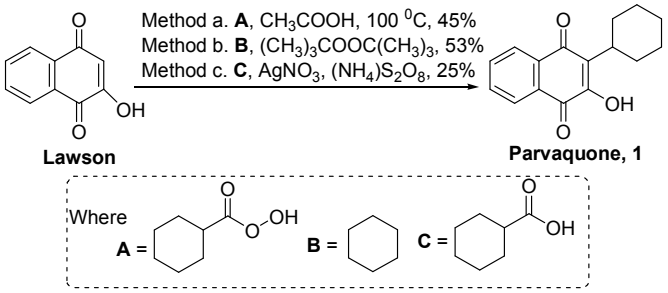
Parvaquone, an antiprotozoal agent against *Theileria parva*, was synthesized in 33.8% overall yield by using cheap and commercial raw materials. Key intermediate, 2-cyclohexyl-1-naphthol was synthesized in 86% yield by cyclohexylation of 1-naphthol and further converted into parvaquone in good yield through reaction sequences such as oxidation, epoxidation followed by isomerization.

Naphthoquinones and substituted naphthoquinones articulate spectrum of wide-ranging biological activities such as antibacterial, antifungal, anti-inflammatory, antithrombotic, antiplatelet, antibiotic, antiallergic, and apoptosis.[1] Naphthoquinones substituted with alicyclic ring at 2 or 3 positions are deliberated as highly effective agents for the suppression of trophozoites in ducks, chickens, canaries and monkeys infected with mosquito or blood-induced malaria. These compounds are capable of destroying fully developed exoerythrocytic forms of malaria parasites.[2]

Theileriosis (*East Coast Fever*), a disease in cattles caused by microscopic parasite *Theileria parva* and majorly found in central and eastern Africa. Theileriosis is among the most concerned livestock diseases in Africa causing an annual loss of 1.1 million cattles and more than 250 million to be at risk.[3] The disease resulted in high mortality rate up to the 1970s due to the lack of effective treatment and mortality can be up to 100%, with death occurring within a month after the initial attachment of infected ticks.[4] 2-cyclohexyl-1,4-naphthoquinone (Parvaquone, **1**) and 2-((4-tert-butylcyclohexyl)methyl)-3-hydroxy-1,4-naphthoquinone (Buparvaquone) have been effectively used since their discovery in the treatment of Theileriosis.[3,4] Parvaquone, marketed as *Clexon,* is an analogue for menoctone which had been identified as having anti-theilerial activity against *Theileria parva*.[5] Unfortunately, due to complexity of structure and high cost of manufacturing prohibited further development of menoctone. Recently, resistance of *Theileria parva* to buparvaquone has been reported.[6] By considering these limitations related with menoctone and buparvaquone, importance of parvaquone is significantly evolving.

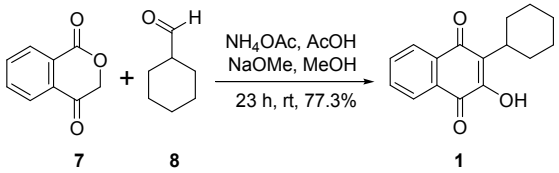
First method for free radical mediated alkylation of naphthoquinone was developed by Fieser et al in 1946 by generation of free radical from corresponding diacyl peroxide in the presence of 2-hydroxy-1, 4-naphthoquinone (Lawson) to give corresponding alkylated naphthoquinones.[7] Developed method provided inferior yield (5 to 6%) of alkylated naphthoquinones and generate numerous side products during the course of reaction. However these protocols were not applied toward synthesis of parvaquone **1**.

In 1951, Fieser et al further developed a method for synthesis of **1** by generating cyclohexyl radical from cyclohexanecarboperoxoic acid **A** in the presence of lawson provide **1** in 45% yield[2] (Scheme 1, Method a). In 1968, Amini et al modified Fieser's general method for alkylation of naphthoquinone by replacing corresponding diacyl peroxide with *tert*-butyl peroxide in respective hydrocarbons and the developed protocol was extended toward synthesis of **1** by using cyclohexane **B** in combination with tert-butyl peroxide in presence of lawson[8] (Scheme 1, Method b). In continuation toward further development, Khambay et al demonstrated new method for synthesis of **1** through generating cyclohexyl radical from cyclohexane carboxylic acid **C** using silver nitrate/ammonium persulfate in the presences of lawson and afforded **1** in 25 % yield[9] (Scheme 1, Method c).



Scheme 1 Different routes for cyclohexyl radical mediated synthesis of parvaquone starting from Lawson.

Besides cyclohexyl radical mediated transformations, new approach for the synthesis of **1** has been disclosed by Leach and Urquhart et al by condensing 1,4-isochromandione **7** with cyclohexanecarbaldehyde **8** followed by rearrangement of resulting aldol product using sodium methoxide in methanol to afford overall 77.3% yield of **1**[10] (Scheme 2).

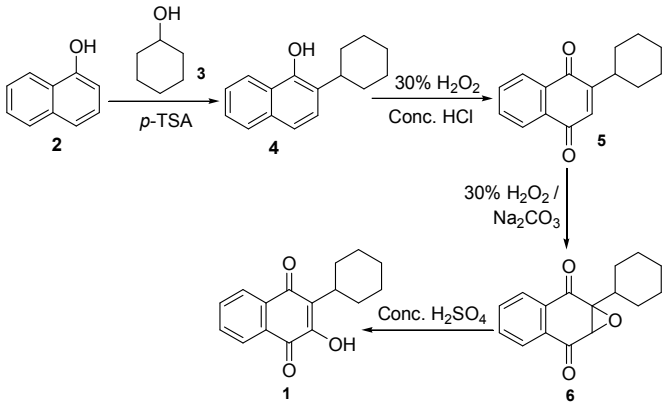


Scheme 2 Synthesis of parvaquone through condensation of 1,4-isochromandione with cyclohexanecarbaldehyde.

Most of these single step transformations for synthesis of **1** retains shortcomings such as necessity of specialized starting materials, use of hazardous peroxides in presence of oxidants, harsh reaction conditions, costly raw materials and afford low yields due to byproduct formations, especially in free radical mediated routes.[2, 8-9]

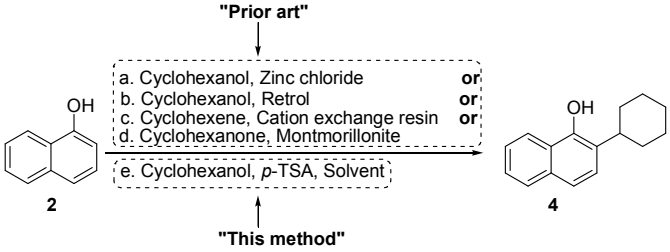
To overcome on aforementioned meagernesses, multistep synthesis through ring construction approach have been recently established by Pena-Carrera et al for synthesis of **1**[11a] and its derivatives[11b] starting from diisopropyl squarate. Use of Grignard reagents, cryogenic reaction conditions, use of trifluoroacetic anhydride, boron tribromide under inert atmosphere restricted this process from being industrially fisible. Considering these inadequacies, the development of adaptable method for synthesis of **1** using cheap raw materials and mild reaction conditions at open atmosphere still remains a significant challenge.

We herein report a simple and effective synthesis of parvaquone developed from cheap and commercially available raw materials. A new reaction system has been established for the synthesis of key intermediate, 2-cyclohexyl-1-naphthol **4**, by cyclohexylation of 1-naphthol **2** using cyclohexanol **3** in presence of *p*-toluenesulfonic acid. Obtained **4** was oxidized by using mild oxidant such as 30% hydrogen peroxide in presence of hydrochloric acid to afford 2-cyclohexyl-1, 4-naphthoquinone **5**. Resulted compound **5** was further converted into parvaquone, **1** by epoxidation followed by isomerization. The general synthetic route is depicted in Scheme 3.



Scheme 3 Synthetic strategy for parvaquone synthesis starting from 1-naphthol.

During literature survey related to synthesis of parvaquone, we identified that the most significant challenge was introduction of cyclohexyl moiety and therefore an alternative key intermediate, **4** was selected toward simplification of cyclohexylation process. Cyclohexylation of naphthol has been reported by catalytic methods using catalysts such as zinc chloride,[12a] (Scheme 4, path a), Retrol (an acid activated bleaching earth)[12b] (Scheme 4, path b), cation exchange resin (Scheme 4, path c),[12c] and montmorillonite[12d] (Scheme 4, path d) in the presence of various cyclohexylating counterparts such as cyclohexanol, cyclohexene and cyclohexanone. Most of these reported methods possesses disadvantages of affording very low yield and necessity of high temperature.

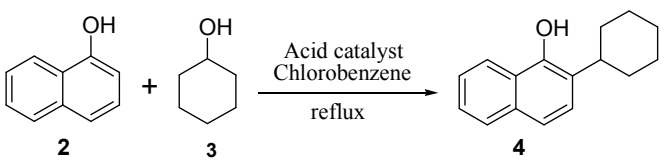


Scheme 4 Different approaches for synthesis of 2-cyclohexyl-1-naphthol.

With this background, we attempted an alternative approach for synthesis of **4**. Based on the preliminary observations from trial experiments, cyclohexanol was chosen as cyclohexylating agent over cyclohexene and cyclohexyl halides. The reactions of **2** with **3** were carried out in solvents such as toluene, xylene and chlorobenzene at their boiling point temperature in the presence of *p*-toluenesulfonic acid (Scheme 4, path e). Among these solvents, chlorobenzene was selected as the best solvent since cyclohexylated product **4** was obtained in highest yield of 86% while toluene and xylene were provided 53% and 42% yields of **4** respectively under the same set of reaction conditions. To our notification, reaction in chlorobenzene below 80 °C did not initiate conversion. When reaction of **2** with **3** was carried out under neat conditions by using *p*-toluenesulfonic acid at 95 °C, desired compound **4** was isolated in 38% yield.

By keeping chlorobenzene constant in the role of reaction solvent, further optimization was carried out to select appropriate acid catalyst for this transformation. The reactions of **2** with **3** were carried out by using various acid catalysts such as *p*-toluenesulfonic acid (*p*-TSA), methanesulfonic acid (MSA), sulfuric acid, tungstate sulfuric acid (TSA) and phosphomolybdic acid and the results are summarized in Table 1. Among the listed acids used, *p*-toluenesulfonic acid mediated cyclohexylation reaction afforded the highest yield of **4** in 86% (Table 1, entry 1) while the lowest yield was obtained from tungstate sulfuric acid mediated cyclohexylation reaction (Table 1, entry 4). Methanesulphonic acid mediated cyclohexylation provided average yield of **4** in 56% (Table 1, entry 2), while inferior yields were isolated from sulfuric acid and phosphomolybdic acid mediated cyclohexylation reactions (Table 1, entry 3 and 5, respectively).

Table 1 Optimization of acid catalyst towards synthesis of 2-cyclohexyl-1-naphthol



Entry	Acid catalyst	Yield (%) **(4)**
1	*p*-Toluenesulfonic acid	86
2	Methanesulfonic acid	56
3	Conc. Sulphuric acid	45
4	Tungstate sulfuric acid	35
5	Phosphomolybdic acid	40

While considering mechanistic aspect for synthesis of **4**, we assume that the reaction could follow general pathway of acid (*p*-TSA, in this case) mediated alkylation of naphthol and might be analogous to other acid catalysed Friedel-Crafts alkylations.[12d,e] Cyclohexyl cation, generated through reaction between cyclohexanol **3** and *p*-TSA, would attack 1- naphthol **2** and followed by rearomatisation to afford 2-cyclohexyl-1-naphthol, **4**.

During screening of reaction sequences for transforming **4** into **1**, reaction conditions developed by Harrity et al[13] were testified and found to provide satisfactory results. Compound **4** was oxidized to 2-cyclohexyl-1, 4-naphthoquinone **5** by using mild oxidant such as 30% hydrogen peroxide in presence of hydrochloric acid at room temperature and provided 68% yield of **5**. Compound **5** was further converted into 2-cyclohexyl-(2, 3)-oxirane-1, 4-naphthoquinone, **6** by using 30% hydrogen peroxide in the presence of aq. sodium carbonate. The reaction was smoothly occurred at room temperature and provided 76% yield of **6**. Isolated epoxide intermediate **6** was then isomerized by using sulfuric acid at room temperature and desired product **1** was isolated in good yield of 76% after work up and purification.

Conclusion

The newly developed synthetic route of parvaquone is having advantages of being operationally simple, environmentally benign and required cheap and commercially accessible raw materials and reagents which might contribute effectively toward cost reduction and making process economically favourable. The intermediates **4**, **5** and **6** were obtained in good yields of 86%, 68% and 76% respectively leading to an overall yield of 33.8%. Use of 30% hydrogen peroxide, industrially accepted green oxidant, under control conditions would make the developed process favourable for scale up when compared with hazardous peroxides under drastic conditions at inert atmosphere.

Acknowledgements

Pravin C. Patil thankful to TEQIP [Technical Education Quality Improvement Program] for financial support for this work.

Notes and references

Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Matunga, Mumbai-400 019, India.
Tel.: +91-22-33612214 fax: +91-22-33611020;
E-mail: kgap@rediffmail.com
[a] Present Address: 2320 S Brook Street, Department of Chemistry, University of Louisville, Louisville, KY-40292, USA.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1. (a) S. Patai, in *The Chemistry of Quinonoid Compounds*, ed. Z. Rappoport, Wiley, New York, 1988, Vol. 2, Parts 1 and 2. (b) R. H. Thomson, in *Naturally Occuring Quinones* IV, Blackie Academic, London, 1997. (c) R. P. Verma, *Anti-Cancer Agents in Med. Chem*., 2006, **6**, 489 and references cited therein. (d) S. Spyroudis, *Molecules*, 2000, **5**, 1291.
2. L. F. Fieser, M. T. Leffler, US Pat., 2 553 648, 1951.
3. R. Bishop, A. Musoke, S. Morzaria, M. Gardner, V. Nene, *Parasitology*, 2004, **129**, 271.
4. (a) M. Mhadhbi, A. Naouach, A. Boumiza, M.-F. Chaabani, S. Ben-Abderazzak, M.-A. Darghouth, *Veterinary Parasitology*, 2010, **169**, 241.
5. N. McHardy, A. T. Hudson, D. W. Morgan, D. G. Rae, T. T. Dolan, *Research in veterinary science*, 1983, **35**, 347.
6. A. Erdemir, M. Aktas, N. Dumanli, D. Turgut-Balik, *Veterinarni Medicina*, 2012, **57**, 559 and references cited therein.
7. L. F. Fieser, US Pat., 2 398 418, 1946.
8. E. S. Huyser, B. Amini, *J. Org. Chem*., 1968, **33**, 576.
9. B. S. Khambay, D. Batty, WO Pat., 9 621 354, 1996.
10. H. Britton, D. Catterick, A. N. Dwyer, A. H. Gordon, S. G. Leach, C. McCormick, C. E. Mountain, A. Simpson, D. R. Stevens, M. W. J. Urquhart, C. E. Wade, J. Warren, N. F. Wooster, A. Zilliox, *Org. Process Res. Dev.*, 2012, **16**, 1607.
11. (a) C. R. Solorio-Alvarado, C. G. Rodriguez-Cendejas, E. Pena-Cabrera, *ARKIVOC*, 2003 (xi), 172. (b) C. R. Solorio-Alvarado, C. Alvarez-Toledano, E. Peña-Cabrera, *ARKIVOC* 2004, (i), 64.
12. (a) B. Alberti, *Justus Liebigs Annalen der Chemie* 1926, **450**, 304. (b) R. P. Perkin, US Pat., 2 125 310, 1936. (c) S. P. Starkov, N. L. Polyanskaya, N. A. Vozhzhova, G. S. Leonova, *Izvestiya Vysshikh Uchebnykh Zavedenii, Khimiya i Khimicheskaya Tekhnologiya* 1977, **20**, 1099. (d) T. Nishimura, S. Ohtaka, A. Kimura, E. Hayama, Y. Haseba, H. Takeuchi, S. Uemura, *Applied Catalysis A: General* 2000, **194-195**, 415. (e) M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* 2010, **6**, No. 6. Published 20 Jan 2010.
13. J. P. A. Harrity, W. J. Kerr, D. Middlemiss, J. S. Scott, *J. Organomet. Chem*., 1997, **532**, 219.
14. L. F. Fieser, M. Fieser, *J. Am. Chem. Soc.*, 1948, **70**, 3177.