Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 48 (2007) 3995–3998

Tetrahedron Letters

Synthesis of 2-hydroxy-3-substituted naphthoquinones using the Heck reaction☆

Alice L. Perez,* G. Lamoureux and Bi Yun Zhen-Wu

Centro de Investigaciones en Productos Naturales (CIPRONA) y Escuela de Química, Universidad de Costa Rica,
2060 San Pedro, San José, Costa Rica

Received 26 January 2007; revised 3 April 2007; accepted 9 April 2007
Available online 14 April 2007

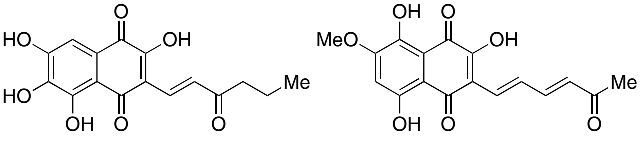
Dedicated to Professor Arturo San Feliciano, in the ocassion of his 60th birthday

---

Abstract—An efficient Heck coupling of 2-hydroxy-3-iodo-naphthoquinone with a series of electron-deficient alkenes in aqueous solution has been accomplished. The method is characterized by simple conditions and facile work-up to isolate the products in good to excellent yields. The products contain the motif present in several naphthoquinone pigments but with enhanced polarity.
© 2007 Published by Elsevier Ltd.

The 1,4-naphthoquinone nucleus is a common substructure in natural products.[1] The 2-hydroxy-3-alkyl substituted naphthoquinones are molecules of interest as pigments[2] and for their wide range of biological activities (this group is well known for its properties as anticancer, antibacterial, antifungal, antimalarial, antitrypanosomal, antileishmanial, insecticidal, and immunostimulant agents).[3,4]

Recently, pigment lindbladione (**1**) was isolated from a *Myxomycete*.[5] Lindbladione is a 3-alkenyl substituted quinone, a motif of interest in our group. Similarly, the insect pathogenic fungi *Cordyceps unilateralis* produces a substituted dienone quinone (**2**) which contains a similar structure (Fig. 1).[6]



1

2

Figure 1. 3-Alkenyl-2-hydroxynaphthoquinones.

We are interested in expanding the variety of groups found on the naphthoquinone nucleus with the hope to increase the water-solubility of these compounds. Our main focus was the modification of the quinone ring of the naphthoquinone since less work has been directed to this strategy. The classic method of synthesis of these derivatives is through the Hooker condensation[7] between 2-hydroxynaphthoquinone (lawsone) and an aldehyde (Fig. 2), but this method is known for its poor yields and the difficult isolation of the product.[8]

With the recent advent of metal catalyzed reactions, a more efficient method was presented. Using a halogenated naphthoquinone as the substrate in a palladium-catalyzed Heck reaction,[9] a series of derivatives can be formed in one step. Although several palladium-catalyzed reactions with quinones or naphthoquinones are known,[10] to our knowledge this is the first example of a Heck coupling on unprotected hydroxyhaloquinones (some aromatic Heck products have been oxidized to quinones).[11]

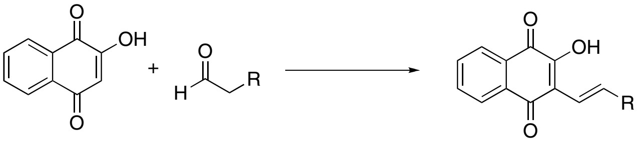


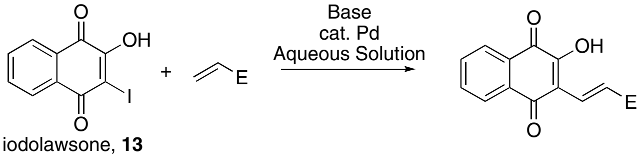
Figure 2. Hooker condensation.

Keywords: Heck reaction; Hooker condensation; Naphthoquinone; 2-Hydroxy-3-iodonaphthoquinone.

☆ Preliminary work was presented at the XIV Simposio Nacional de Química Orgánica, Rosario, Argentina, November 9–12, 2003.

* Corresponding author. Tel.: +506 207 3031; fax: +506 225 9866; e-mail: alperez@cariari.ucr.ac.cr

0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.04.033



iodolawsone, **13**

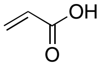
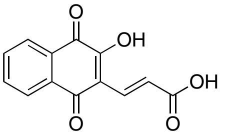
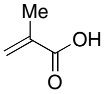
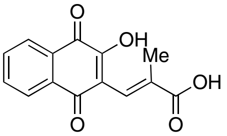
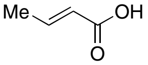
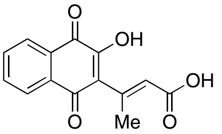
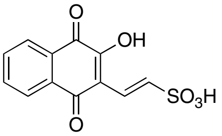
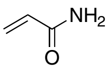
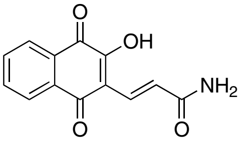
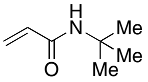
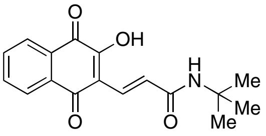
Figure 3. General reaction scheme for the Heck coupling.

To optimize the reaction, we first had to investigate the conditions, the reagents and the substrates suitable for the Heck reaction. We found that 2-hydroxy-3-iodonaphthoquinone (iodolawsone, **13**)[12] is the best substrate for the model reaction with acrylic acid (Fig. 3). Even though no reaction took place at room temperature, at 100 °C (reflux) the reaction was usually complete within 4 h. We chose water as the perfect solvent as it provided a safe and 'green' medium for the reaction and, moreover, allowed the use of 'ligandless' conditions (i.e., without expensive phosphine ligands that might need to be eliminated at the end of the reaction).[13]

The reaction was insensitive to the type of base, as long as there were at least 2 equiv (one to deprotonate the acidic OH in iodolawsone, the other for the catalytic cycle). We were gratified to see that our choice of water was justified by the complete solubility of the deprotonated iodolawsone during the reaction and the easy separation of the solid product during work-up by simple acidification and filtration. However, this process limited our study to small, polar alkenes that would be easy to remove after work-up. Our optimized results are shown in Table 1.

In the reactions using carboxylic acids (Table 1, entries 1–4), an excess of base was required to neutralize the acid. The sulfonic acid is commercially available as a 1 M solution of the sodium salt so we used this reactant directly as the solution. The yield in this case was lower, probably due to the high solubility of the product imparted by the sulfonic acid group. We had excellent success with unsaturated amides (Table 1, entries 5–6) but we were surprised to observe the sublimation of the

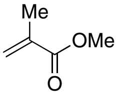
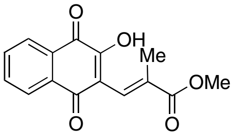
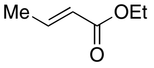
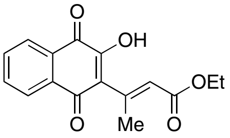
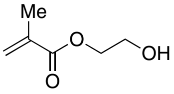
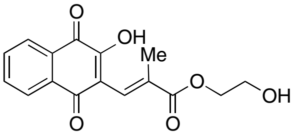
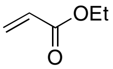
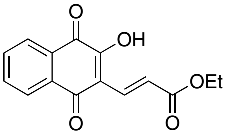
Table 1. Heck coupling between iodolawsone and unsaturated acids and amides

Entry	Substrate	Base	Time (h)	Yield (%)	Product
1	 (2 equiv)	K_2CO_3 (5 equiv)	4	72	 **3**
2	 (2.5 equiv)	K_2CO_3 (5 equiv)	4	78	 **4**
3	 (2.5 equiv)	K_2CO_3 (5 equiv)	5	71	 **5**
4	 [a] (11 equiv)	K_2CO_3 (3 equiv)	2	62	 **6**
5	 (2 equiv)	K_2CO_3 (3 equiv)	6	95	 **7**
6	 (2 equiv)	K_2CO_3 (3 equiv)	6	41	 **8**

All reactions were conducted in reflux under a nitrogen atmosphere with 5 mol % $Pd(OAc)_2$ as catalyst. All compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy.

[a] Used as a 1 M solution in water directly without the addition of more solvent.

Table 2. Heck coupling between iodolawsone and unsaturated esters

Entry	Substrate	Base/co-solvent	Time (h)	Yield (%)	Product
1	 (3 equiv)	Hünig (2.5 equiv) 50% MeOH	3	80	 **9**
2	 (3 equiv)	Hünig (2.5 equiv) 50% EtOH	4	32	 **10**
3	 (3 equiv)	Hünig (2.5 equiv) 50% ethylene glycol	7	68	 **11**
4	 (3 equiv)	Hünig (2.5 equiv) 50% EtOH	2.5	86	 **12**

All reactions were conducted in reflux under a nitrogen atmosphere with 5 mol % $Pd(OAc)_2$ as catalyst. All compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy.

tert-butylamide during the reaction, which may have contributed to the low yield. In all cases, as expected in the Heck reaction, the products only contain a trans (or *E*) double bond, clearly identifiable in the spectroscopic data.

However successful these conditions were for acids and amides, we could not use the same procedure to couple acrylic esters or acrylonitriles to iodolawsone without the presence of polymeric impurities and significant hydrolysis of the ester to the carboxylic acid. Further investigation revealed that a co-solvent[14] was necessary to dissolve the ester without forming polymer. The greatest difference was seen in the selection of base[15]-with K_2CO_3 complete hydrolysis to the carboxylic acid was seen but with an amine base (*N*-ethyl-*N*,*N*-diisopropylamine, Hünig's base) we isolated only the ester.[16] The results are presented in Table 2.

In the case of the esters, the yield depends on the steric hindrance at the β-position; ethyl crotonate (Table 2, entry 2) gave much lower yields than the other substrates. Hydroxyethyl methacrylate (entry 3) also gave product in reduced yields, probably due to losses during work-up because of the greater water solubility.

In summary, we have presented an efficient and practical method to couple the 2-hydroxy-1,4-naphthoquinone nucleus to a variety of polar groups. The catalytic reaction does not require long reflux times, special ligands nor protecting groups, and the product is isolated by simple filtration, yielding pure compounds without the need for chromatographic separation. We are continuing our work in the field of naphthoquinones, using other Pd-catalyzed reactions to form a variety of substrates.

Acknowledgments

We are grateful to the Vice Presidency of Research University of Costa Rica (Project No. 809-98-231), the International Foundation for Science (IFS, Project No. F/33441) and the Organization for the Prohibition of Chemical Weapons (OPCW), for financial support, to Ms. L. Hernández, Natural Products Research Center, University of Costa Rica for her technical assistance and to Dr. Víctor H. Soto and the Universidad de Santiago de Compostela at Lugo, Spain for high resolution mass spectrometry data.

Supplementary data

Experimental procedures and full spectroscopic data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.033.

References and notes

1. Thomson, R. H. *Naturally Occurring Quinones*; Academic Press: New York, 1971.

2. Karci, F.; Ertan, N. *Coloration Tech.* **2005**, *121*, 153.
3. da Silva, M. N.; Ferreira, V. F.; de Souza, M. C. B. V. *Quim. Nova* **2003**, *26*, 407.
4. (a) Oliveira, A. B.; Raslan, D. S.; Khuong-Huu, F. *Tetrahedron Lett.* **1990**, *31*, 6873; (b) Wagner, H.; Kreher, B.; Lotter, H.; Hamburger, M. O.; Cordell, G. A. *Helv. Chim. Acta* **1989**, *72*, 659; (c) Hudson, A. T.; Randall, W. U.S. patent No. 5,175,319, 1992; (d) Khambay, B. P. S.; Jewess, P. *Crop Protection* **2000**, *19*, 597; (e) Sendl, A.; Chen, J. L.; Jolad, S. D.; Stoddart, C.; Rozhon, E.; Kernan, M.; Nanakorn, W.; Balick, M. *J. Nat. Prod.* **1996**, *59*, 808; (f) Khambay, B. P. S.; Batty, D.; Beddie, D. G.; Denholm, I.; Cahill, M. R. *Pest. Sci.* **1997**, *50*, 291; (g) Vanelle, P.; Terme, Th.; Giraud, L.; Crozet, M. P. *Tetrahedron Lett.* **2001**, *42*, 391; (h) Ball, M. D.; Bartlett, M. S.; Shaw, M.; Smith, J. W.; Nasr, M.; Meshnick, S. R. *Antimicrob. Agents Chemother.* **2001**, 1473; (i) Camara, C. A.; Pinto, A. C.; Rosa, M. A.; Vargas, M. D. *Tetrahedron* **2001**, *57*, 9569; (j) Oliveira, M. F.; Lemos, T. L. G.; de Mattos, M. C.; Segundo, T. A.; Santiago, G. M. P.; Braz-Filho, R. *An. Acad. Bras. Cien.* **2002**, *74*, 211; (k) De Moura, K. C. G.; Emery, F. S.; Neves-Pinto, C.; Pinto, M. C. F. R.; Dantas, A. P.; Salomão, K.; de Castro, S. L.; Pinto, A. V. *J. Braz. Chem. Soc.* **2001**, *12*, 325; (l) da Silva, M. N.; da Souza, M. C. B. V.; Ferreira, V. F.; Pinto, A. V.; Pinto, M. C. R. F.; Wardell, S. M. S. V.; Wardell, J. F. *Arkivoc* **2003**, *10*, 156.
5. Ishikawa, Y.; Ishibashi, M.; Yamamoto, Y.; Hayashi, M.; Komiyama, K. *Chem. Pharm. Bull.* **2002**, *50*, 1126.
6. (a) Kittakoop, P.; Punya, J.; Kongsaeree, P.; Lertwerawat, Y.; Jintasirikul, A.; Tanticharoen, M.; Thebtaranonth, Y. *Phytochemistry* **1999**, *52*, 453; (b) Isaka, M.; Kittakoop, P.; Kirtikara, K.; Hywel-Jones, N. L.; Thebtaranonth, Y. *Acc. Chem. Res.* **2005**, *38*, 813.
7. (a) Hooker, S. C. *J. Chem. Soc.* **1896**, *69*, 1356; (b) Hooker, S. C. *J. Am. Chem. Soc.* **1936**, *58*, 1163.
8. For a recent example, see: Nagabhushana, K. S.; Ameer, F.; Green, I. R. *Synth. Commun.* **2001**, *31*, 719.
9. Reviews: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009; (b) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379; (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771.
10. For Sonogashira coupling, see: (a) Shvartsberg, M. S.; Barabanov, I. I.; Fedenok, L. G. *Russ. Chem. Rev.* **2004**, *73*, 161, and references cited therein; For Stille coupling, see: (b) Stagliano, K. W.; Malinakova, H. C. *J. Org. Chem.* **1999**, *64*, 8034, and references cited therein; For Suzuki coupling, see: (c) Best, W. M.; Sims, C. G.; Winslade, M. *Aust. J. Chem.* **2001**, *54*, 401, and references cited therein.
11. Mital, A.; Lad, R.; Thakur, A.; Singh Negi, V.; Ramachandran, U. *Arkivoc* **2006**, 99–106.
12. Pérez, A. L.; Lamoureux, G.; Herrera, A. *Synth. Commun.* **2004**, *34*, 3389.
13. Yao, Q.; Kinney, E. P.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 7528.
14. Phase-transfer catalysts did not decrease the amount of polymer but did accelerate the reaction (complete reaction in 1 h). The co-solvent was varied for each reaction to prevent transesterification of the esters.
15. We also tried KOAc and K_3PO_4 as bases without success. See Ref. 13 for a comparison of bases in the Heck reaction.
16. For the use of diisopropylamine as base to prevent ester hydrolysis in a Heck reaction, see: Nájera, C.; Gil-Moltó, J.; Karlstrum, S.; Falvello, L. R. *Org. Lett.* **2003**, *5*, 1451.