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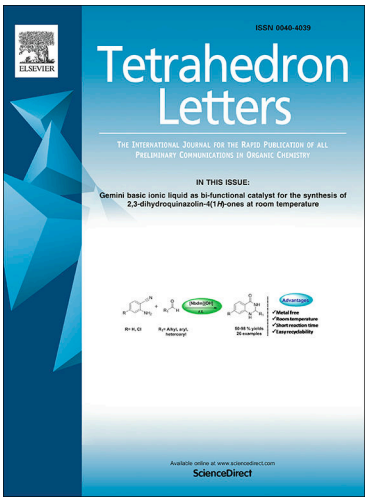

The one-pot synthesis of amidonapthoquinones from aminonaphthoquinones

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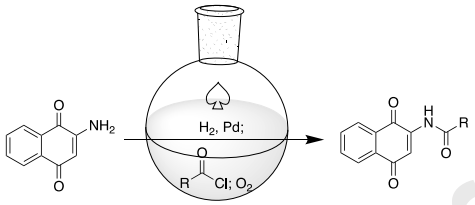

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The one-pot synthesis of amidonapthoquinones from aminonaphthoquinones

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ABSTRACT

Described here is a one-pot method of synthesizing amidonaphthoquinones from the corresponding aminonaphthoquinones. The scope of amides that can be synthesized using this methodology is relatively broad and the yield of product is higher than the traditional methods of synthesizing these substrates.

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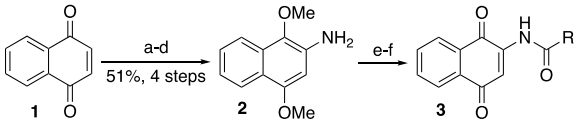
1. Introduction

Amidonaphthoquinones are found in a number of natural products and biologically relevant molecular targets.[1] However, their synthesis from the corresponding aminonaphthoquinones has generally been problematic. That the nitrogen atom is part of a vinylogous amide is undoubtedly responsible for this lack of reactivity.[1] As a consequence, amidonaphthoquinones are commonly generated from the corresponding protected aminohydroquinones followed by deprotection and oxidation (Scheme 1). As an example of such a strategy, DeBrabander and co-workers recently synthesized the amidonaphthoquinone of salinisporamycin by generating the amide from the hydronaphthoquinone and subsequently oxidizing the hydroquinone.[2] They turned to this indirect strategy only after struggling to couple the aminonapthoquinone with the requisite carboxylic acid. While they do not explicitly state their examination of the necessary aminonaphthoquinone, Lang and Groth applied a similarly circuitous synthesis of the amidonaphthoquinone marcanine A.[3] Finally, during our recent study of naphthoquinone acrylamide photoelectrocyclization reactions we suffered through low yielding amide formation from the coupling of 2-aminonaphthoquinone with acids or acid chlorides and were forced to adopt the more roundabout DeBrabander route to provide the desired substrates (Scheme 1).[4]

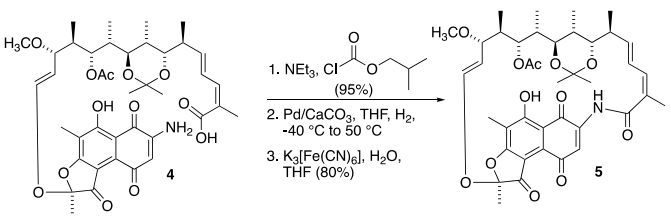


a. H_2, 10% Pd/C (10% w.t.), THF, r.t., 3h; b. NaH, DMF, 0 ˚C, 1h, then Me_2SO_4, 0˚C to r.t., 16h; c. HNO_3-SiO_2, CH_2Cl_2, r.t., 15 min; d. H_2, 10% Pd/C (10% w.t.), EtOH, r.t., 8h, (51% overall (steps a-d)); e. RCOOH, EDC•HCl, 4-DMAP, CH_2Cl_2, r.t., or RCOCl, NEt_3, CH_2Cl_2, r.t.; f. CAN, MeCN/H_2O, r.t., 5-15 min.

Scheme 1 Synthesis of amidoquinone through aminohydroquinone.[4]

2. Results and discussion

In an effort to improve upon this multistep protocol, we considered whether a one-pot aminonaphthoquinone reduction, amide formation, and aerobic oxidation sequence might be more successful and were encouraged that Corey and Clark had previously communicated a related approach during their generation of the rifamycin *ansa*-lactam. As outlined in Scheme 2, they reduced the rifamycin aminonaphthoquinone using $Pd/CaCO_3$ and H_2, filtered the catalyst away from the resulting hydroquinone, and then converted it into the desired rifamycin *ansa*-lactam by heating the reaction mixture to 50 °C. Oxidation of the hydroquinone using potassium ferricyanide enabled them to convert it to naphthoquinone **5**.[5] In light of the importance of amidonaphthoquinones, it was surprising to us that in the years subsequent to the Corey work that the *in situ* reduction protocol has not been examined in any significant detail.



Scheme 2. Corey and Clark's Reductive Macrocyclization to the Rifamycin Ansalactam.[5]

To get a sense of whether the one-pot process could be used to generate the amidonaphthoquinones of interest to us, we initially examined whether a modified Corey/Clark protocol could be applied to 2-aminonaphthoquinone **7** to give acrylamide **10** (Scheme 3). We synthesized aminoquinone **7**, the starting compound for the one-pot protocol, in 83% overall yield from

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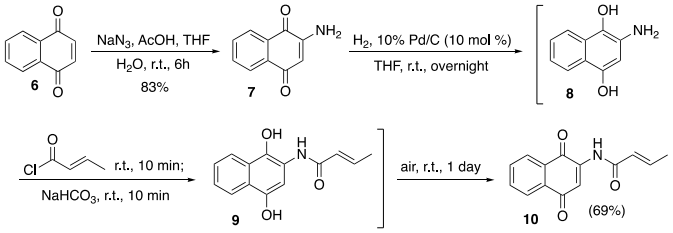
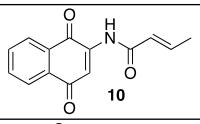
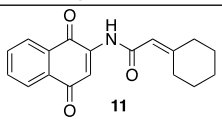
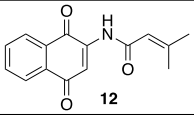
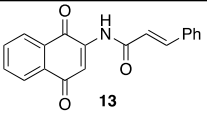
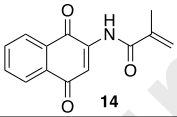
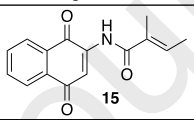
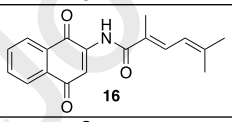
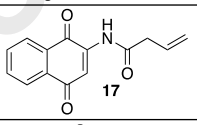
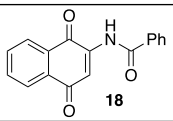
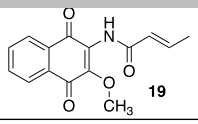
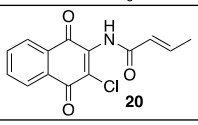
1,4-naphthoquinone. [c]Used 2 equivalent of acid chloride. [d]Not determined.

found that the *in situ* reduction, coupling, oxidation sequence worked well. Our optimized conditions involved the sequential hydrogenation of the quinone using 10% Pd/C and H_2 (1 atm), a N_2 purge to replace the remaining H_2, the rapid addition of crotonyl chloride and $NaHCO_3$, filtration to remove the Pd/C and $NaHCO_3$, and exposure of the reaction mixture to the atmosphere.[14] This sequence gave amidonaphthoquinone **10** in 69% yield. To put this result into perspective, the synthesis of **10** using the 6-step approach that was outlined in Scheme 1 required 5 chromatographic purifications and gave **10** in 29% overall yield.



Scheme 3. One-Pot Synthesis of Acrylamide **10** via the *in situ* Reduction of Aminonaphthoquinone **7**.

Table 1. One-Post Amide Couplings-Substrate Scope.

Entry	Product	1-pot yield[a,b]	6-step yield
1	 **10**	69% (57%)	29%
2	 **11**	70% (58%)	30%
3	 **12**	66% (55%)	41%
4	 **13**	72% (60%)	33%
5	 **14**	71%[c] (59%)	23%
6	 **15**	71%[c] (59%)	39%
7	 **16**	40%[c,] (33%)	-----[d]
8	 **17**	73% (61%)	32%
9	 **18**	79% (66%)	41%
10	 **19**	77%	-----[d]
11	 **20**	51%	-----[d]

[a]Isolated yield from compound **7**. [b]Yields in parentheses are calculated from 1,4-naphthoquinone. [c]Used 2 equivalent of acid chloride. [d]Not determined.

We next explored the scope of the sequence (Table 1). As illustrated, a range of acid chlorides were amenable to the protocol giving overall yields that were significantly higher than the multi-step approach.[7] Of note was that the reactions were relatively simple to perform, they did not require the purification of the intermediates, they generally did not result in alkene reduction, that sensitive substrates like dienamide **16** could be generated,[10] and that β,γ-unsaturated amidonaphthoquinone **17** did not undergo isomerization using this protocol.[11] Limiting at this stage was that these conditions appear to be restricted to the use of acid chlorides; the use of EDC in the coupling of **8** with crotonic acid resulted in a 19% yield of **10**. Also limiting in instances where the acid chloride might be valuable was that substrates having an α-substituent required the use of 2 equivalents of the acid chlorides to obtain yields that were acceptable (entries 5-7).

We also were able to convert napthoquinones having substitution at the 3-position into the corresponding acrylamides. Specifically, 2-amino-3-methoxy and 2-amino-3-chloronaphthaquinones were converted into acrylamides **19** and **20**,[8,9] respectively, in good overall yields thus demonstrating some of the scope for this methodology (entries 10 and 11).[12,13]

To summarize, we have optimized and examined the scope of a one-pot method of synthesizing 2-amidonaphthoquinone derivatives from aminonapthoquinones. This method was shown to be generally superior when compared to stepwise approaches to this family of substrates. We will continue to utilize and optimize this protocol.

Acknowledgments

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8. For the synthesis of the aminoquinone that leads to **19** see: (a) Brandy, Y.; Brandy, N.; Akinboye, E.; Lewis, M.; Mouamba, C.; Mack, S.; Butcher, R.; Anderson, A.J.; Bakare, O. Synthesis and Characterization of Novel Unsymmetrical and Symmetrical 3-Halo- or 3-Methoxy-substituted 2-Dibenzoylamino-1,4-naphthoquinone Derivatives. *Molecules* **2013**, *18*, 1973-1984. (b) Bakare, O.; Ashendel, C.L.; Peng, H.; Zalkow, L.H.; Burgess, E.M. Synthesis and MEK1 inhibitory activities of imido-substituted 2-Chloro-1,4-naphthoquinone. *Bioorg. Med. Chem.* **2003**, *11*, 3165-3170.
9. For the synthesis of the aminoquinone that leads to **20** see: Diaz, R.; Reyes, O.; Francois, A.; Leiva, A.M.; Loeb, B. Synthesis of a new polypyridinic highly conjugated ligand with electron-acceptor properties. *Tetrahedron Lett.* **2001**, *43*, 5353-6467.
10. (*E*)-*N*-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,5-dimethylhexa-2,4-dienamide (**16**). mp 169-173 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (broad s, 1H), 8.10 (dd, *J* = 7.8, 1.1 Hz, 2H), 7.91 (s, 1H), 7.77 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 7.71 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 7.36 (d, *J* = 11.6 Hz, 1H), 6.16 (d, *J* = 11.6 Hz, 1H), 2.07 (s, 3H), 1.94 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.4, 181.6, 168.0, 146.3, 140.4, 135.1, 133.4, 133.3, 132.4, 130.1, 126.7, 126.5, 126.3, 120.9, 116.8, 27.2, 19.2, 12.6; IR (neat) 3370, 2916, 2861, 1665, 1641, 1628, 1590, 1578, 1503, 1477, 1446, 1380, 1333, 1297, 1226, 1199, 1157, 1095 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1287, found 296.1293.
11. *N*-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)but-3-enamide (**17**). mp 158-160 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (broad s, 1H), 8.10 (partially obscured dd, *J* = 7.7, 0.9 Hz, 1H), 8.09 (partially obscured dd, *J* = 7.7, 1.2 Hz, 1H), 7.85 (s, 1H), 7.78 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1H), 7.71 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 6.02 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.40 (dd, *J* = 10.4, 1.0 Hz, 1H), 5.37 (dd, *J* = 17.2, 1.3 Hz, 1H) 3.27 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.3, 181.2, 170.0, 139.9, 135.1, 133.4, 132.3, 130.1, 129.8, 126.8, 126.6, 121.5, 117.4, 43.1; IR (neat) 3202, 3069, 1; HRMS (ESI) calcd. for $C_{14}H_{12}NO_3$ $[M+H]^+$ 242.0817, found 242.0824.
12. (*E*)-*N*-(3-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)but-2-enamide (**19**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.3 Hz, 1H), 8.04 (d, *J* = 7.2 Hz, 1H), 7.72 (dd, *J* = 7.1, 7.1 Hz, 1H), 7.69 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.39 (broad s, 1H), 7.00 (dq, *J* = 15.2, 6.9 Hz, 1H), 6.07 (d, *J* = 15.3 Hz, 1H), 4.18 (s, 3H), 1.93 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.4, 181.4, 163.5, 150.3, 143.2, 134.2, 133.9, 131.6, 130.5, 127.0, 126.7, 126.4, 124.7, 60.6, 18.1. IR (neat) 3243, 3015, 1669, 1640, 1620, 1593, 1582, 1525, 1445, 1336, 1317, 1300, 1264, 1213, 1193, 1041, 1010, 966 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{14}NO_4$ $[M+H]^+$ 272.0923, found 272.0925.
13. (*E*)-*N*-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)but-2-enamide (**20**). mp 116-117 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.0, 1.2 Hz, 1H), 8.12 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.79 (ddd, *J* = 7.3, 7.3, 1.2 Hz, 1H), 7.76 (ddd, *J* = 7.4, 7.4, 1.3 Hz, 1H), 7.71 (broad s, 1H), 7.08 (dq, *J* = 15.2, 6.9 Hz, 1H), 6.09 (dd, *J* = 15.2, 1.5 Hz, 1H), 1.97 (dd, *J* = 6.9, 1.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.1, 177.8, 162.2, 145.0, 139.4, 135.0, 134.2, 132.8, 131.8, 130.4, 127.7, 127.2, 124.4, 18.3; IR (neat) 3247, 1687, 1669, 1647, 1616, 1591, 1515, 1334, 1308, 1288, 1249, 1206, 1101, 977 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{10}NO_3Na^{35}Cl$ $[M+Na]^+$ 298.0247, found 298.0252; calcd. for $C_{14}H_{10}NO_3Na^{37}Cl$ $[M+Na]^+$ 300.0217, found 300.0232.
14. General procedure for the hydrogenation coupling oxidation protocol: To a solution of 2-amino-1,4-naphthaquinone (87 mg, 0.5 mmol) in THF (6 mL) at rt was added 10% Pd/C (9 mg). The resulting mixture was charged with H_2 gas (1 atm) and allowed to stir overnight. After this time period the H_2 balloon was removed and the reaction mixture was purged with N_2 for 5 min. To the resulting reaction mixture was added a solution of the acid chloride (0.55 or 1.00 mmol) in CH_2Cl_2 (2 mL) via syringe. The resulting mixture was stirred at rt for 10 min and $NaHCO_3$ (46 mg, 0.55 mmol or 84 mg, 1 mmol) was added. After stirring for an additional 10 min the reaction mixture was passed through a short pad of Celite using EtOAc (20 mL). The filtrate was then exposed to the atmosphere at rt for 1 day. The reaction mixture was concentrated and the resulting residue was purified using flash column chromatography (hexanes:ethyl acetate).

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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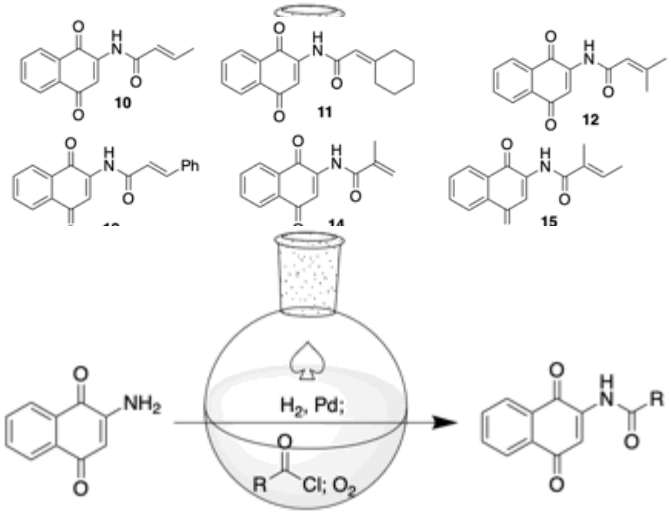

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