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# Unexpected reaction of 2-amino-1,4-naphthoquinone with aldehydes: new synthesis of naphtho[2,1-*d*]oxazole compounds

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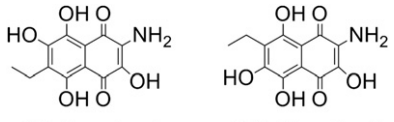
ABSTRACT

Treatment of 3-substituted 2-amino-1,4-naphthoquinones **3** with an aldehyde in a solution of hydrobromic acid in acetic acid led to 2,4-disubstituted naphtho[2,1-*d*]oxazol-5-ols. The outcome of this simple conversion is even more remarkable in view of the very similar reactions reported in literature, which all give rise to completely different products. Furthermore, the acquired naphthoxazoles **5**–**11** could be oxidatively ring opened by means of PIFA or CAN into a series of *N*-acylated 2-amino-1,4-naphthoquinones. A synthetic pathway towards 2-substituted naphtho[2,3-*d*]oxazole-4,9-diones was also disclosed as the outcome of CAN mediated oxidation of a 4-chloronaphtho[2,1-*d*]oxazol-5-ol.



## 1. Introduction

Quinone and naphthoquinone moieties are prevalent motifs in various natural products, which are associated with diverse biological activities.[1] Among the naphthoquinones, 2-amino-1,4-naphthoquinone derivatives are interesting molecules because of their molluscicidal,[2] cytotoxic,[3] anti-tumor[4] and antibacterial[5] activities. The 2-amino-1,4-naphthoquinone moiety can be even found in natural products, such as echinamines A (**1**) and B (**2**)[6] from the sea urchin *Scaphechinus mirabilis* and hygrocins A and B[7] from *Streptomyces hygroscopicus* (Fig. 1).




**1** Echinamine A **2** Echinamine B

**Fig. 1.**

Besides, 2-amino-1,4-naphthoquinone may serve as a synthetic precursor for benzo[*b*]acridine-6,11-diones,[8–10] benzo[*f*]indole-4,9-diones,[8–11] 1*H*-1-azaanthracene-9,10-diones[12] and 1,2,3,4-tetrahydrobenzo[*g*]quinazoline-5,10-diones.[13] The reactions of 2-amino-1,4-naphthoquinone (**3a**) as nucleophile have received only little attention, which is presumably due to the amide like character of the amino group in **3a**. An example of the bidendate nucleophilic character of 2-amino-1,4-naphthoquinone (**3a**) can be found in the reaction of **3a** with electrophiles such as methyleniminium salts. The *N*-aminomethyl compounds initially formed by kinetic control are subsequently converted to the thermodynamically more stable *C*-Mannich reaction products.[13] In some cases the nucleophilicity of the amino group is greater than may be expected from a vinylogous amide. For example, 2-amino-1,4-naphthoquinone (**3a**), reacts as an *N*-nucleophile with β-ketoesters bis-dielectrophiles giving rise to anilides that can be cyclized to 2-oxo-1*H*-1-azaanthraquinones.[12] *C*-Alkylated 2-amino quinone derivatives are obtained by reaction 2-amino-1,4-naphthoquinone with dimethylacetylene dicarboxylate[14] or copper(I) bromide catalyzed Michael addition reaction with methyl vinyl ketone and 2-propenal.[15]

As a result of their importance in medicinal chemistry, a large number of quinone derivatives and related compounds have been synthesized in order to explore for novel bioactive agents with enhanced pharmacological properties. In continuation of our interest on new syntheses[16] of 1,4-naphthoquinones we wish to report on a new methodology for the reaction of 2-amino-1,4-naphthoquinones **3** with aldehydes.

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## 2. Results and discussion

In the course of our research towards new azaanthraquinones we needed 2-amino-3-alkenyl-1,4-naphthoquinones **4**. Inspired by the synthesis of 2-hydroxy-3-(prop-2-enyl)-1,4-naphthoquinone from 2-hydroxy-1,4-naphthoquinone,[17] 2-amino-1,4-naphthoquinone (**3a**) was reacted with 5 equiv of propanal in the presence of a 0.23 M hydrogen bromide solution in acetic acid at 75–80 °C. After acid base workup and extraction with diethyl ether a white-grey powder was obtained. $^1$H NMR-analysis of this product indicated the absence of typical olefinic protons in the 5–7 ppm region, and suggested the formation of another compound other than the expected naphthoquinone **4**. Complete spectral investigation of this compound by means of both 1-D ($^1$H NMR, $^{13}$C NMR) and 2-D (HMBC and HMQC) NMR allowed us to assign the structure as 2-ethyl-5-hydroxynaphtho[2,1-*d*]oxazole (**5**). The reaction of **3a** with 1 equiv of propanal in 0.23 M hydrogen bromide solution in acetic acid at room temperature and a simplification of the workup procedure allowed an improvement of the yield from 50 to 74%. Since the purity of the reaction product was higher when using an excess of aldehyde all the following annulations of 2-aminonaphthoquinone were performed with 5 equiv of aldehyde. The treatment of **3a** with substituted aliphatic aldehydes and benzaldehyde, gave rise to 2-substituted 5-hydroxynaphtho[2,1-*d*]oxazoles **5**–**8** in moderate yields (Scheme 1). In general, these hydroxynaphtho[2,1-*d*]oxazoles could be simply purified by high vacuum evaporation to remove traces of aldehydes, leaving the products in purities of over 95%. The reaction of 2-aminonaphthoquinone (**3a**) with acetaldehyde however, only led to starting material. Most likely the volatility of acetaldehyde is the reason for this. Next, 3-substituted 2-amino-1,4-naphthoquinones **3b**–**d** were reacted with pivaldehyde in a 0.23 M hydrogen bromide solution in acetic acid at room temperature. The 2,4-disubstituted 5-hydroxynaphtho[2,1-*d*]oxazoles **9**–**11** were obtained in 80–97% yields and did not require further purification (Scheme 1).

Some closely related naphthoxazoles, like neosalvianen **12**[18] and salviamines B–D **13**[19] have been isolated from several medicinal Salvia species. Several other 5-oxygenated naphtho[1,2-*d*]oxazoles, e.g., **14**, derivatives of lapachol, display trypanocidal activity (Fig. 2).[20]

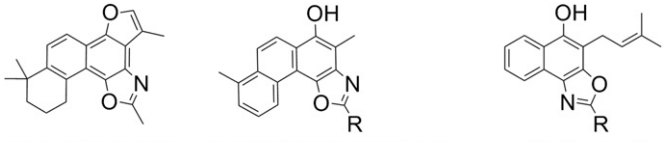
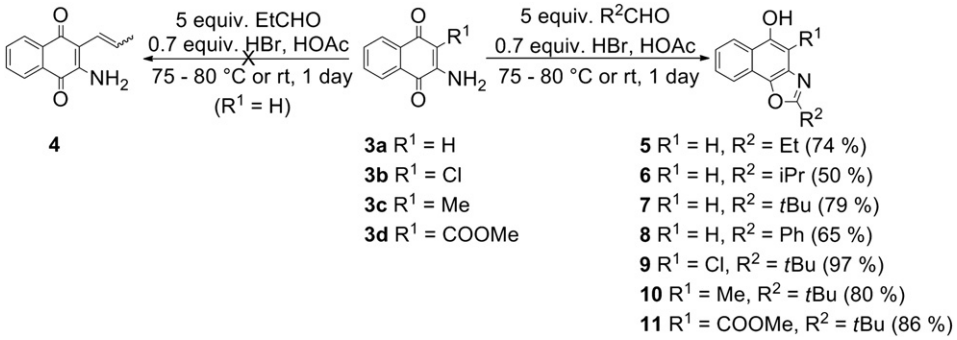
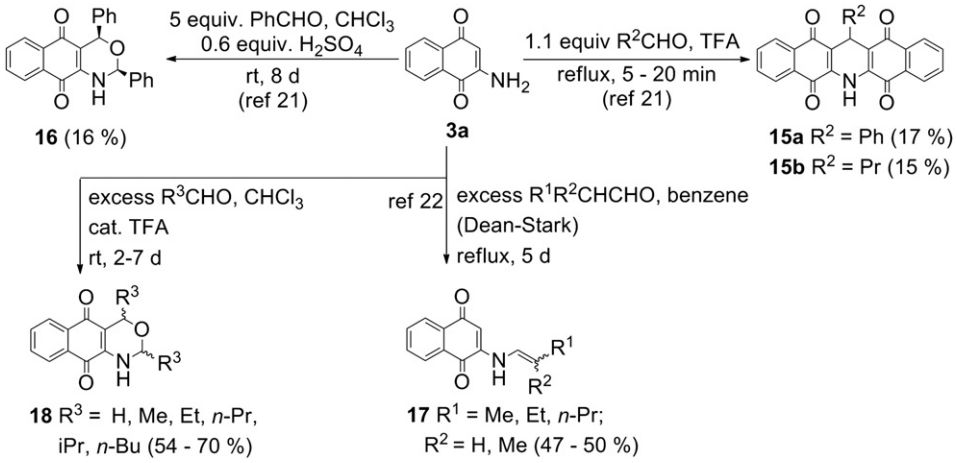



**Fig. 2.**

The formation of these naphtho[2,1-*d*]oxazoles was completely unexpected since a previously reported reaction of 2-aminonaphthoquinone with butanal or benzaldehyde in an excess of TFA leads to 6,13-dihydro-6-azapentacene-5,7,12,14-tetraones **15** in low yields. According to the literature, by changing the acid to sulfuric acid, 2,4-diphenyl-1*H*-2,4-dihydronaphtho[2,3-*d*]1,3-oxazine-5,10-dione (**16**) was formed.[21] Under neutral conditions 2-amino-1,4-naphthoquinone (**3a**) reacts with aldehydes to give *N*-(alkenyl)aminoquinones **17** in 47–56% yield, while a catalytic amount of trifluoroacetic acid generates a diastereomeric mixture of 2,4-dialkyl-1*H*-2,4-dihydronaphtho[2,3-*d*]1,3-oxazine-5,10-diones **18** (Scheme 2).[22] Compounds **15** and **16**, though in very low



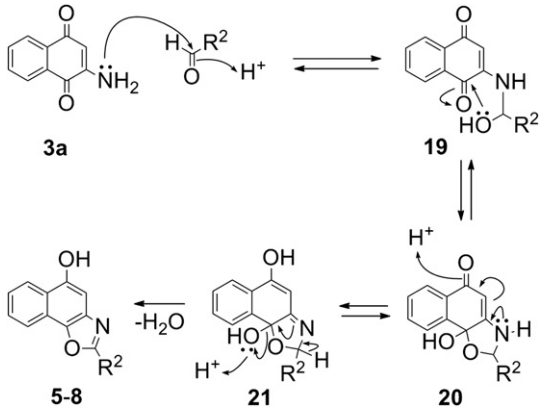

**Scheme 1.**




**Scheme 2.**

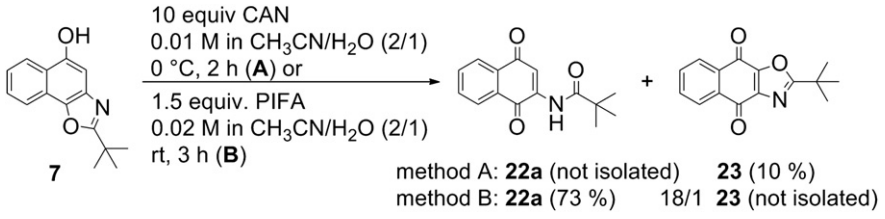
yields, were produced under very concentrated reaction conditions (approximately 1 mmol of quinone/ml solvent), which might explain the fact that 2 mol of aldehyde were incorporated in **16** and 2 mol of quinone in **15**.

Clearly the mechanism of formation of the naphtho[2,1-*d*]oxazoles **5**–**11** is different from that of the related reactions in Scheme 2. Most likely, a hemi-aminal **19** is formed, which upon a 5-*exo*-*trig* attack of the hydroxyl group to the $C_1$=O carbonyl resulted in an oxazolidine ring **20**. A subsequent electron delocalisation towards $C_4$=O (compound **21**) followed by an elimination of water gave the oxazole ring annulated to the α-naphthol as the characteristic structural feature of **5**–**11** (Scheme 3). The reaction of 2-aminonaphthoquinone with 2-butanone in 0.23 M hydrogen bromide solution in acetic acid at room temperature only afforded starting material.




**Scheme 3.**

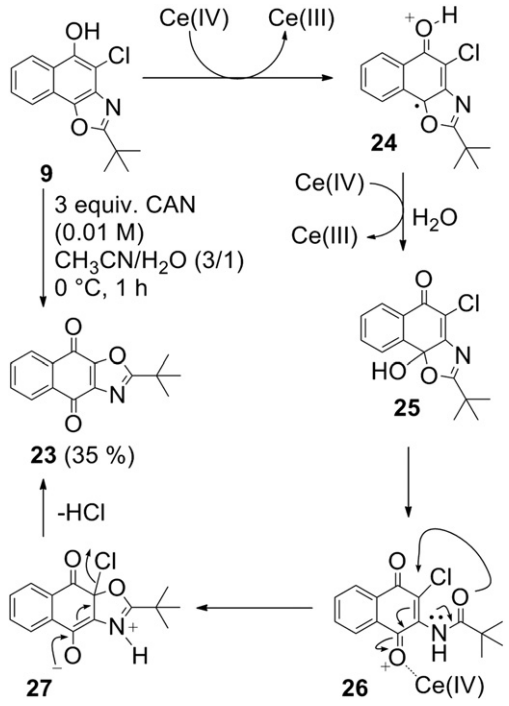
Next, the oxidation reaction of **7** with different oxidising agents was investigated. The reaction of **7** ($R^1$=H, $R^2$=$^t$Bu) with 1–3 equiv of cerium(IV) ammonium nitrate (CAN) in aqueous acetonitrile at 0 °C afforded a tarry reaction mixture containing varying ratio's of 2-(pivaloylamino)-1,4-naphthoquinone **22a**, a rearranged oxazole **23** and an unknown compound. The formation of **22a** and this unknown compound could be avoided by using a large excess of 10 equiv of CAN under dilute conditions. After flash chromatography, 2-*tert*-butylnaphtho[2,3-*d*]oxazole-4,9-dione (**23**) could be isolated in only 10% yield (Scheme 4).




**Scheme 4.**

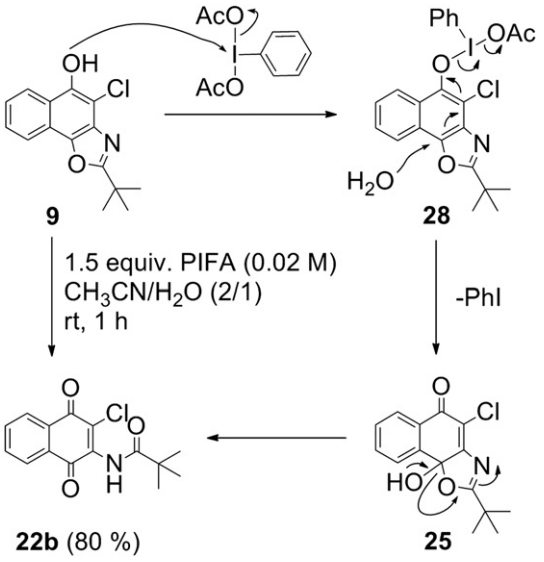
Hypervalent iodine reagents, e.g., [bis(trifluoroacetoxy)iodo] benzene (PIFA) are frequently used to oxidize phenols,[23] because of the mild reaction conditions, good oxidation performances and low toxicity.[24] Indeed, the reaction of **7** with 1.5 equiv of PIFA in aqueous acetonitrile led to an 18/1 (LC-MS) mixture of 2-(pivaloylamino)-1,4-naphthoquinone (**22a**) and 2-*tert*-butylnaphtho[2,3-*d*]oxazole-4,9-dione (**23**) (Scheme 4). Increasing the amount of PIFA to 2.5 equiv did not lead to further conversion of **22a** into **23**.

2-*tert*-Butylnaphtho[2,3-*d*]oxazole-4,9-dione (**23**) could be prepared in a more convenient way by treating **9** ($R^1$=Cl, $R^2$=$^t$Bu) with 3 equiv of CAN in aqueous acetonitrile at 0 °C. Compound **23** could be separated from two unknown compounds by means of flash chromatography and was obtained in 35% yield (Scheme 5). Compound **9**, which can be regarded as a hydroquinone monoalkyl ether will undergo an initial one-electron oxidation leading to the electrophilic cation-radical **24**, which eventually is attacked by a molecule of water to give the hydrate (not shown). A second one-electron oxidation leads to a cation, which is attacked by water to give **25**.[25] Ring opening of **25** gives the 2-acylaminonaphthoquinone **22b**, which upon Lewis acid catalysis by Ce(IV)[26] will undergo an intramolecular 1,4-addition of the amide oxygen to the α,β-unsaturated enone. Elimination of HCl in **27** finally yields the naphtho[2,3-*d*]oxazole-4,9-dione **23**. In case of the CAN oxidation of compound **7** also an intramolecular nucleophilic attack on the enone system occurs, but instead of HCl elimination the aromatic oxazole is formed by air oxidation.



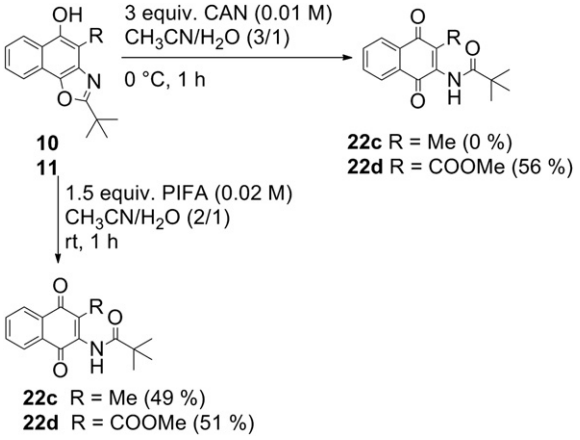

**Scheme 5.**

On the other hand, by the oxidation of **9** with 1.5 equiv of PIFA 3-chloro-2-(pivaloylamino)-1,4-naphthoquinone (**22b**) was isolated as the sole product in excellent yield after flash chromatography (Scheme 6). The mechanism of the PIFA oxidation presumably involves initial ligand exchange at the iodine(III) center of PIFA.[27] This intermediate **28** is then trapped by a water molecule and after reductive elimination of iodobenzene leads to the product **25**, which finally ring opens to give **22b**. In this case the absence of a Lewis acid prevents the further intramolecular nucleophilic attack of oxygen on the enone system.




**Scheme 6.**

Encouraged by this result **10** ($R^1$=Me, $R^2$=$^t$Bu) was also reacted with 3 equiv of CAN, but this led to a complex reaction mixture, which could not be further elucidated. The milder reaction of **10** and **11** with 1.5 equiv of PIFA furnished 3-methyl-2-(pivaloylamino) naphthoquinone **22c** and **22d** as the only products in an excellent crude yield (83–87%, 90% purity by HPLC). After flash chromatography on silica gel the yields dropped drastically to 49% and 51%, respectively. The 4-methoxycarbonylnaphtho[2,1-*d*]oxazole **11**, could also be completely converted into the *N*-acylated 2-aminonaphthoquinone **22d** upon treatment with CAN. Because of the rather large drop in yield (56%) after flash chromatography on silica gel, an alternative purification of **14d** on neutral alumina was attempted, but quantitative hydrolysis of the amide occurred, furnishing the initial starting product **3d** in 31% yield (Scheme 7).




**Scheme 7.**

## 3. Conclusions

A versatile procedure was discovered towards 2,4-disubstituted naphtho[2,1-*d*]oxazol-5-ols **5**–**11** and consisted in treating 3-substituted 2-amino-1,4-naphthoquinones **3** with an aldehyde in a solution of hydrobromic acid in acetic acid. The outcome of this simple reaction is even more remarkable in view of the very similar reactions reported in literature, which all give rise to completely different products. Apparently the type of acid and the concentration of reagents used in this condensation are of prime importance. Furthermore, the acquired naphthoxazoles could be oxidatively ring opened by means of PIFA or CAN into a series of *N*-acylated 2-amino-1,4-naphthoquinones **22**. A synthetic pathway towards 2-substituted naphtho[2,3-*d*]oxazole-4,9-diones **23** was also disclosed as the outcome of CAN mediated oxidation of a 4-chloronaphtho[2,1-*d*]oxazol-5-ol **9**.

## 4. Experimental section

### 4.1. General experimental methods

$^1$H NMR spectra were recorded on a Bruker Avance DRX 250 spectrometer at 250 MHz or a Bruker Avance II 500 spectrometer at 500 MHz with internal standard TMS. $^{13}$C NMR spectra were recorded on a Bruker Avance DRX 250 spectrometer at 63 MHz, Bruker Avance II 500 spectrometer at 125 MHz with internal standard $CDCl_3$ ($\delta$=77). $^{13}$C NMR assignments were made using DEPT spectra. Melting points were determined on a Büchi melting point apparatus B-540 and are uncorrected. GC–MS analyses were performed using an Intersience GC 8000 series gas chromatograph with an EC™-5 column (length: 30 m, internal diameter: 0.32 mm, film thickness: 0.25 μm). Products were injected in a split injector (250 °C); the inert carrier gas is helium. The mass spectrometer was a Fisons Instruments MD 800 using electron impact (70 eV) as ionization method. HRMS was measured with a VGQuattro II mass spectrometer. Infrared spectra were recorded with an Avatar 370 FT-IR apparatus (Thermo Nicolet), using the attenuated total reflection technology. Column chromatography was performed using Merck silica (diameter 40–63 μm). TLC-analysis was performed on glass-backed plates (Merck) coated with 0.2 mm silica $60F_{254}$. Amino naphthoquinones **3a**,[28] **3c**[28] and **3d**[29] were prepared according to literature procedures.

### 4.2. Reaction of 2-amino-1,4-naphthoquinones with aldehydes: general procedure

2-Amino-1,4-naphthoquinone **3a** (100 mg, 0.56 mmol) was dissolved in acetic acid (2 mL), after which a 33% solution of HBr in acetic acid (0.1 mL) and the aldehyde (2.8 mmol) were added dropwise. It is important to prevent evaporation of the aldehyde by means of a reflux condenser. The reaction mixture was stirred at room temperature from 24 h to 48 h and followed to completion by TLC (Petroleum ether/EtOAc, 2/1). After completion the reaction mixture was diluted with water and extracted with diethyl ether. The combined organic extracts were washed with aqueous sodium bicarbonate, aqueous sodium sulphite and brine. Drying over $MgSO_4$, followed by filtration and concentration in vacuo gave the corresponding product in moderate to good yield and more than 95% purity (HPLC). Eventually recrystallisation may be performed in $Et_2O$/heptane.

*4.2.1. 2-Ethyl-5-hydroxynaphtho[2,1-d]oxazole (**5**).* Yield: 74%. Light brown powder, mp 208.3–208.7 °C. $^1$H NMR (250 MHz, DMSO): $\delta$ 1.39 (3H, t, $J$=7.5 Hz, $CH_2CH_3$), 3.01 (2H, q, $J$=7.5 Hz, $CH_2CH_3$), 7.10 (1H, s, 4-CH), 7.49 (1H, ddd, $J$=1.3, 7.0, 8.4 Hz, 7-CH), 7.64 (1H, ddd, $J$=1.3, 6.9, 8.2 Hz, 8-CH), 8.05 (1H, d, $J$=8.1 Hz, 9-CH), 8.23 (1H, d, $J$=8.1 Hz, 6-CH), 10.26 (1H, s, OH). $^{13}$C NMR (62.90 MHz, DMSO): $\delta$ 10.9 ($CH_3$), 21.5 ($CH_2$), 99.2 (4-C), 119.3 (9-C), 119.7 (5a-C), 122.6 (9a-C), 123.4 (6-C), 124.2 (8-C), 127.4 (7-C), 137.5 (3a-C), 139.2 (9b-C), 150.7 (5-C), 167.0 (2-C). IR (KBr, $cm^{-1}$): $\nu$ 1586, 1639, 3157. MS (70 eV, $m/z$ (%)): 214 ($[M+1]^+$, 46), 213 ($[M]^+$, 100), 212 (93), 130 (54), 105 (47), 102 (91), 101 (67), 76 (54), 75 (48). HRMS (ESI): $m/z$ calcd for $C_{13}H_{11}NO_2+H^+$: 214.0863; found 214.0856.

*4.2.2. 2-Isopropyl-5-hydroxynaphtho[2,1-d]oxazole (**6**).* Yield: 50%. Dark red powder, mp 171.7–172.3 °C. $^1$H NMR (400 MHz, DMSO): $\delta$ 1.43 (6H, d, $J$=6.9 Hz, $CH(CH_3)_2$), 3.33 (1H, septet, $J$=6.9 Hz, *CH*

$(CH_3)_2$), 7.11 (1H, s, 4-CH), 7.50 (1H, ddd, $J$=1.2, 7.0, 8.3 Hz, 7-CH), 7.64 (1H, ddd, $J$=1.1, 7.0, 8.1 Hz, 8-CH), 8.06 (1H, d, $J$=8.0 Hz, 9-CH), 8.26 (1H, d, $J$=8.0 Hz, 6-CH), 10.25 (1H, s, OH). $^{13}$C NMR (100.60 MHz, DMSO): $\delta$ 20.3 (CH($CH_3$)$_2$), 28.2 ($CH$($CH_3$)$_2$), 99.2 (4-C), 119.3 (9-C), 119.7 (5a-C), 122.6 (9a-C), 123.4 (6-C), 124.2 (8-C), 127.3 (7-C), 137.3 (3a-C), 139.1 (9b-C), 150.7 (5-C), 170.0 (2-C). IR (ATR, cm$^{-1}$): $\nu$ 1580, 1643. MS (70 eV, $m/z$ (%)): 228 ([M+1]$^+$, 13), 227 ([M]$^+$, 99), 226 (37), 212 (100), 185 (10), 105 (22), 102 (44), 101 (20), 77 (17), 76 (19), 75 (16).

*4.2.3. 2-tert-Butyl-5-hydroxynaphtho[2,1-d]oxazole (**7**).* Yield: 79%. Light brown powder, mp 203.5–204.1 °C. $^1$H NMR (250 MHz, DMSO): $\delta$ 1.49 (9H, s, C($CH_3$)$_3$), 7.10 (1H, s, 4-CH), 7.50 (1H, ddd, $J$=1.3, 7.0, 8.4 Hz, 7-CH), 7.64 (1H, ddd,=1.2, 6.9, 8.2 Hz, 8-CH), 8.10 (1H, d, $J$=7.9 Hz, 9-CH), 8.35 (1H, d, $J$=8.3 Hz, 6-CH), 10.25 (1H, s, OH). $^{13}$C NMR (62.90 MHz, DMSO): $\delta$ 28.3 (C($CH_3$)$_3$), 33.8 ($C$($CH_3$)$_3$), 99.2 (4-C), 119.3 (9-C), 119.7 (5a-C), 122.6 (9a-C), 123.4 (6-C), 124.2 (8-C), 127.3 (7-C), 136.7 (3a-C), 139.1 (9b-C), 150.5 (5-C), 172.0 (2-C). IR (ATR, cm$^{-1}$): $\nu$ 1582, 1644. MS (70 eV, $m/z$ (%)): 242 ([M$^+$1]$^+$, 39), 241 ([M]$^+$, 82), 227 (40), 226 (85), 185 (100), 130 (64), 105 (55), 102 (70), 101 (49), 77 (42), 57 (58). HRMS (ESI): $m/z$ calcd for $C_{15}H_{15}NO_2$+H$^+$: 242.1176; found 242.1183.

*4.2.4. 2-Phenyl-5-hydroxynaphtho[2,1-d]oxazole (**8**).* Yield: 65%. Dark brown powder, mp (decomp.) 181.2–181.6 °C. $^1$H NMR (250 MHz, DMSO): $\delta$ 7.19 (1H, s, 4-CH), 7.46–7.75 (5H, m, $CH_{arom.}$), 7.92–7.95 (2H, m, $CH_{arom.}$), 8.22–8.30 (2H, m, $CH_{arom.}$), 10.41 (2H, s, OH). $^{13}$C NMR (62.90 MHz, DMSO): $\delta$ 99.6 ($CH_{arom.}$), 120.2 ($CH_{arom.}$), 124.1 ($CH_{arom.}$), 125.3 ($C_{quat.}$), 127.3 ($CH_{arom.}$), 128.2 ($CH_{arom.}$), 129.0 (2×$CH_{ar}$), 129.7 ($CH_{arom.}$), 129.8 ($CH_{arom.}$), 131.8 ($C_{quat.}$), 133.3 ($CH_{arom.}$), 138.9 ($C_{quat.}$), 140.0 ($C_{quat.}$), 151.9 (5-C), 162.1 ($C_{quat.}$), 167.8 (2-C). IR (ATR, cm$^{-1}$): $\nu$ 1583, 1597, 1683. MS (70 eV, $m/z$ (%)): 263 ([M+2]$^+$, 2), 262 ([M+1]$^+$, 19), 261 ([M]$^+$, 100), 130 (39), 104 (22), 102 (74), 77 (16), 76 (20), 75 (14), 73 (13). HRMS (ESI): $m/z$ calcd for $C_{17}H_{11}NO_2$+H$^+$: 262.0863; found 262.0852.

*4.2.5. 2-tert-Butyl-4-chloro-5-hydroxynaphtho[2,1-d]oxazole (**9**).* Yield: 97%. Orange-brown powder, mp 127.8–128.8 °C. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 1.57 (9H, s, $CH_3$), 5.97 (1H, s, OH), 7.54 (1H, ddd, $J$=1.4, 7.0, 8.4 Hz, $CH_{arom.}$), 7.64 (1H, ddd, $J$=1.3, 6.8, 8.2 Hz, $CH_{arom.}$), 8.14 (1H, dd, $J$=1.1, 9.0 Hz, $CH_{arom.}$), 8.32 (1H, dd, $J$=1.3, 8.2 Hz, $CH_{arom.}$). $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 28.8 (C($CH_3$)), 34.6 ($C$($CH_3$)$_3$), 104.8 ($C_{quat.}$), 119.1 ($C_{quat.}$), 119.9 ($CH_{arom.}$), 122.3 ($C_{quat.}$), 123.3 ($CH_{arom.}$), 125.4 ($CH_{arom.}$), 127.4 ($CH_{arom.}$), 134.8 ($C_{quat.}$), 141.0 ($C_{quat.}$), 145.1 (5-C), 173.6 (2-C). IR (ATR, cm$^{-1}$): $\nu$ 758, 846, 914, 1014, 1142, 1203, 1418, 1450, 1544, 2969. MS (ES) $m/z$ (%): 276 (M+H$^+$, 100), 278 (M+3). HRMS (ESI): $m/z$ calcd for $C_{15}H_{14}ClNO_2$+H$^+$: 276.0786; found 276.0781.

*4.2.6. 2-tert-Butyl-5-hydroxy-4-methylnaphtho[2,1-d]oxazole (**10**).* Yield: 80%. Dark red powder, mp 122.4–123.7 °C. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 1.49 (9H, s, C($CH_3$)$_3$), 2.48 (3H, s, $CH_3$), 5.11 (1H, s, OH), 7.49 (1H, ddd, $J$=1.4, 6.9, 8.3 Hz, $CH_{arom.}$), 7.56 (1H, ddd, $J$=1.2, 6.9, 8.0 Hz, $CH_{arom.}$), 7.93 (1H, dd $J$=0.6, 8.8 Hz, $CH_{arom.}$), 8.18 (1H, dd, $J$=0.4, 9.1, Hz, $CH_{arom.}$). $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 10.9 ($CH_3$), 28.8 (C($CH_3$)$_3$), 35.8 ($C$($CH_3$)$_3$), 110.5 ($C_{quat.}$), 119.8 ($C_{quat.}$), 120.4 ($CH_{arom.}$), 124.3 ($CH_{arom.}$), 125.8 ($C_{quat.}$), 126.2 ($CH_{arom.}$), 127.7 ($CH_{arom.}$), 136.2 ($C_{quat.}$), 141.2 ($C_{quat.}$), 149.1 (5-C), 174.4 (2-C). IR (ATR, cm$^{-1}$): $\nu$ 755, 960, 1065, 1354, 1546, 2973. MS (ES) $m/z$ (%): 256 (M+H$^+$, 100). HRMS (ESI): $m/z$ calcd for $C_{16}H_{17}NO_2$+H$^+$: 256.1332; found 256.1339.

*4.2.7. 2-tert-Butyl-5-hydroxy-4-methoxycarbonylnaphtho[2,1-d]oxazole (**11**).* Yield: 86%. White powder, mp 150.3–151.1 °C. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 1.57 (9H, s, C($CH_3$)$_3$), 4.14 (1H, s, $OCH_3$), 7.53 (1H, ddd, $J$=1.2, 7.1, 8.4 Hz, $CH_{arom.}$), 7.72 (1H, ddd, $J$=1.2, 7.0, 8.2 Hz, $CH_{arom.}$), 8.20 (1H, d, $J$=8.1 Hz, $CH_{arom.}$), 8.43 (1H, d, $J$=8.4 Hz, $CH_{arom.}$), 12.5 (1H, s, OH). $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 28.7 (C($CH_3$)$_3$), 34.5 ($C$($CH_3$)$_3$), 52.9 ($OCH_3$), 99.0 ($C_{quat.}$), 119.8 ($CH_{arom.}$), 122.8 ($C_{quat.}$), 123.3 ($C_{quat.}$), 125.2 ($CH_{arom.}$), 125.4 ($CH_{arom.}$), 125.8 ($C_{quat.}$), 130.3 ($CH_{arom.}$), 130.8 ($C_{quat.}$), 134.2 ($C_{quat.}$), 160.0 (5-C), 171.6 (2-C or CO), 173.2 (CO or 2-C). IR (ATR, cm$^{-1}$): $\nu$ 706, 757, 803, 1049, 1142, 1253, 1349, 1439, 1556, 1647, 2971. MS (ES) $m/z$ (%): 300 (M+H$^+$, 100). HRMS (ESI): $m/z$ calcd for $C_{17}H_{17}NO_4$+H$^+$: 300.1230; found 300.1221.

### 4.3. CAN oxidation—general procedure

The oxazole (0.2 mmol) was suspended in an acetonitrile/water (3:1) (2 mL) mixture and cooled to 0 °C, after which cerium ammonium nitrate (0.6 mmol) was added. The reaction mixture was stirred for 1 h at 0 °C and subsequently quenched with water and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The obtained residue was if needed purified by flash chromatography on silica gel.

*4.3.1. 2-tert-Butylnaphtho[2,3-d]oxazole-4,9-dione (**23**).* This compound has been prepared before.[30] Complete spectral data are given here.

$R_f$=0.05 (petroleum ether/EtOAc: 6/1). Yield: 35%. Yellow powder, mp 135–136 °C. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 1.50 (9H, s, $CH_3$), 7.54 (1H, ddd, $J$=3.2, 5.6, 7.7 Hz, $CH_{arom.}$), 7.73–7.70 (2H, m, $CH_{arom.}$), 8.14 (1H, dd, $J$=1.7, 7.7 Hz, $CH_{arom.}$). $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 28.4 (C($CH_3$)), 34.4 ($C$($CH_3$)), 87.4 ($C_{quat.}$), 122.9 ($CH_{arom.}$), 126.2 ($C_{quat.}$), 129.3 ($C_{quat.}$), 131.0 (2×$CH_{arom.}$), 135.4 ($CH_{arom.}$), 158.8 ($C_{quat.}$), 173.5 ($C_{quat.}$), 180.0 (CO), 184.2 (CO). IR (ATR, cm$^{-1}$): $\nu$ 695, 784, 906, 1103, 1201, 1569, 1585, 1680, 2974. MS (ES$^+$) $m/z$ (%): 256 (M+H$^+$, 100). HRMS (ESI): $m/z$ calcd for $C_{15}H_{13}NO_3$+H$^+$: 256.0968; found 256.0958.

*4.3.2. 2-Methoxycarbonyl-3-(pivaloylamino)-1,4-naphthoquinone (**22d**).* $R_f$=0.33 (petroleum ether/EtOAc: 2/1). Yield: 56%, mp 113.1–113.9 °C. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 1.34 (9H, s, C($CH_3$)$_3$), 3.95 (3H, s, $OCH_3$), 7.78 (2H, ddd, $J$=1.6, 7.0, 8.7 Hz, 6-CH and 7-CH), 8.11 (2H, ddd, $J$=1.5, 6.0, 8.1 Hz, 5-CH and 8-CH). $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 27.1 (C($CH_3$)), 40.5 ($C$($CH_3$)$_3$), 52.7 ($OCH_3$), 121.9 ($C_{quat.}$), 126.7 ($CH_{arom.}$), 126.9 ($CH_{arom.}$), 129.4 ($C_{quat.}$), 131.7 ($C_{quat.}$), 133.7 ($CH_{arom.}$), 135.6 ($CH_{arom.}$), 136.1 ($C_{quat.}$), 164.0 (CO), 176.5 (CO), 181.4 (CO), 181.6 (CO). IR (ATR, cm$^{-1}$): $\nu$ 713, 743, 789, 953, 971, 1118, 1157, 1286, 1488, 1661, 1704, 1734, 3355. MS (ES) $m/z$ (%): 316 (M+H$^+$, 100). HRMS (ESI): $m/z$ calcd for $C_{17}H_{17}NO_5$+H$^+$: 316.1179; found 316.1168.

### 4.4. PIFA oxidation—general procedure

The oxazole (0.42 mmol) was dissolved in a mixture of acetonitrile/water (2:1) (21 mL), with some MeOH (175 μl, 2.5 v/v$H_2O$ %). 1.5 equiv of PIFA was added and the reaction mixture was allowed to stir for the indicated amount of time at room temperature. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The collected residue was further purified by flash chromatography on silica gel.

*4.4.1. 2-(Pivaloylamino)-1,4-naphthoquinone (**22a**).* $R_f$=0.13 (petroleum ether/EtOAc: 4/1). Yield: 73%. Yellow powder, mp 199.3–199.9 °C. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 1.35 (9H, s, C($CH_3$)$_3$), 7.72 (1H, d×pseudo t, $J$=1.5, 7.5 Hz, 6-CH or 7-CH), 7.79 (1H, d×pseudo t, $J$=1.6, 7.6 Hz, 7-CH or 6-CH), 7.86 (1H, s, 2-CH), 8.11 (2H, dd, $J$=1.8, 7.3 Hz, 5-CH and 8-CH), 8.73 (1H, broad s, NH). $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 27.3 (C($CH_3$)$_3$), 40.6 ($C$($CH_3$)$_3$), 116.9 ($CH_{arom.}$), 119.3 ($C_{quat.}$), 126.4 ($CH_{arom.}$), 126.6 ($CH_{arom.}$), 132.2 ($C_{quat.}$), 133.2 ($CH_{arom.}$), 135.0 ($CH_{arom.}$), 140.0 ($C_{quat.}$), 177.9 (CO), 181.5 (CO), 185.2 (CO). IR (ATR, cm$^{-1}$): $\nu$ 724, 789, 886, 1105, 1201, 1297, 1336, 1477, 1497,

1644, 1704, 2964, 2983, 3374. MS ($ES^+$) *m*/*z* (%): 258 ($M+H^+$, 100). HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}NO_3+H^+$: 258.1125; found 258.1132.

*4.4.2. 2-Chloro-3-(pivaloylamino)-1,4-naphthoquinone (**22b**).* $R_f$=0.15 (petroleum ether/EtOAc: 4/1). Yield: 80%. Yellow powder, mp 140.6–141.4 °C. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ 1.38 (9H, s, $C(CH_3)$), 7.75 (1H, d×pseudo t, *J*=1.9, 7.0 Hz, 6-CH or 7-CH), 7.79 (1H, d×pseudo t, *J*=1.9, 7.0 Hz, 7-CH or 6-CH), 7.92 (1H, broad s, NH), 8.09–8.13 and 8.18–8.20 (2×1H, 2×m, 5-CH and 8-CH). $^{13}C$ NMR (62.90 MHz, $CDCl_3$): $\delta$ 27.4 ($C(CH_3)$), 40.5 ($C(CH_3)$), 127.0 ($CH_{arom.}$), 127.5 ($CH_{arom.}$), 130.3 ($C_{quat.}$), 131.6 ($C_{quat.}$), 134.1 ($CH_{arom.}$), 134.8 ($CH_{arom.}$), 139.6 ($C_{quat.}$), 175.2 (CO), 177.7 (CO), 180.1 (CO). IR (ATR, $cm^{-1}$): $\nu$ 714, 787, 1104, 1464, 1483, 1590, 1661, 1704, 1969, 3333. MS (ES) *m*/*z* (%): 292 ($M+H^+$, 100), 294 (M+3, 20). HRMS (ESI): *m*/*z* calcd for $C_{15}H_{14}ClNO_3+H^+$: 292.0735; found 292.0731.

*4.4.3. 2-Methyl-3-(pivaloylamino)-1,4-naphthoquinone (**22c**).* $R_f$=0.28 (petroleum ether/EtOAc: 4/1). Yield: 49%. Yellow powder, mp 109.6–110.8 °C. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.37 (9H, s, $C(CH_3)_3$), 2.06 (3H, s, $CH_3$), 7.69 (1H, d×pseudo t, *J*=1.1, 7.4 Hz, 6-CH or 7-CH), 7.73 (1H, d×pseudo t, *J*=1.2, 7.4 Hz, 7-CH or 6-CH), 8.05 (1H, dd, *J*=0.9, 7.4 Hz, 5-CH or 8-CH), 8.11 (2H, d, *J*=7.6 Hz, 8-CH or 5-CH and NH overlap). $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 14.5 ($CH_3$), 27.5 ($C(CH_3)$), 40.3 ($C(CH_3)_3$), 126.2 ($CH_{arom.}$), 126.7 ($CH_{arom.}$), 130.5 ($C_{quat.}$), 132.5 ($C_{quat.}$), 133.3 ($CH_{arom.}$), 134.4 ($CH_{arom.}$), 135.3 ($C_{quat.}$), 138.1 ($C_{quat.}$), 176.4 (CO), 182.2 (CO), 184.8 (CO). IR (ATR, $cm^{-1}$): $\nu$ 714, 793, 1137, 1196, 1293, 1458, 1478, 1654, 1692 $cm^{-1}$. MS ($ES^+$) *m*/*z* (%): 272 ($M+H^+$, 100). HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}NO_3+H^+$: 272.1281; found 272.1289.

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## Supplementary data

Copies of $^1H$ NMR and $^{13}C$ NMR spectra for compounds **5**–**11**, **22a**–**d** and **23** are included in the Supplementary data. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2010.10.082. These data include MOL files and InChIKeys of the most important compounds described in this article.

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