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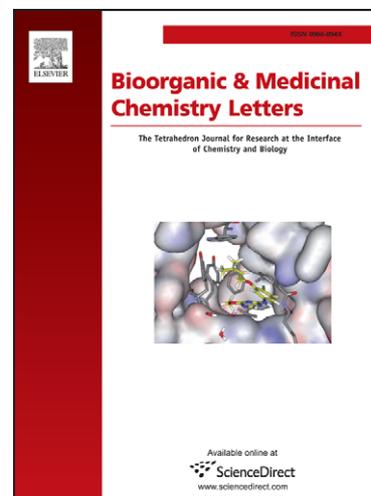
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Reaction of Naphthoquinones with Substituted Nitromethanes. Facile Synthesis and antifungal activity of Naphtho[2,3-*d*]isoxazole-4,9-diones

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Abstract— We report here a simple entry into naphtho[2,3-*d*]isoxazole-4,9-dione system containing a EWG in position 3 using the readily available 2,3-dichloro-1,4-naphthoquinone and nitromethyl derivatives in the presence of base. Antifungal activity of synthesised naphthoquinones was evaluated against ATCC and PYCC reference strains of *Candida*. The results suggest that the naphtho[2,3-*d*]isoxazole-4,9-dione scaffold has the potential to be developed into novel and safe therapeutic antifungal agents.

Compounds containing the quinone group represent an important class of biologically active molecules that are widespread in nature.¹ Isoxazoles also have a significant number of biological applications, displaying hypoglycemic, analgesic, anti-inflammatory, antifungal, anti-bacterial and HIV-inhibitory activity.² Naphtho[2,3-*d*]isoxazole-4,9-diones **1** (Figure 1) combine both functionalities and are an attractive target. Importantly,³ compounds **1** also display agricultural applications.

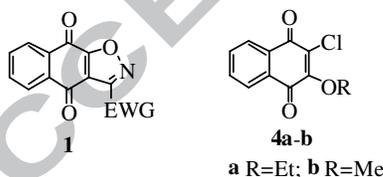


Figure 1. Structure of compounds **1** and **4**.

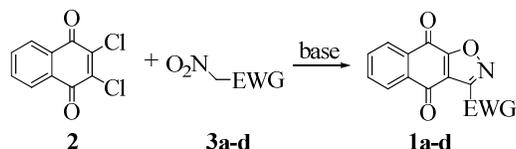
To date, most of the routes to naphtho[2,3-*d*]isoxazole-4,9-diones described in the literature use *in situ* generation of nitrile oxides, require the synthesis of the necessary starting materials and do not allow the introduction of electron-withdrawing group (EWG) in position 3.⁴⁻⁶ To the best of our knowledge, there is only one route that introduces an ethyl ester in position 3 of the isoxazole moiety that involves a manganese (III) acetate initiated reaction between readily available 1,4-naphthoquinones and ethyl nitroacetate. This

method is highly wasteful, requiring 8 eq. of ethyl nitroacetate and 12 eq. of manganese (III) acetate.^{7,8}

Recently we described naphtho[2,3-*d*]isoxazole-4,9-dione-3-carboxylates **1a-b** as potent, non-cytotoxic, antiapoptotic agents, through modulation of apoptotic pathways.⁹ The two compounds were synthesized from 1 eq. of each commercially available starting material, 2,3-dichloro-1,4-naphthoquinone **2** and a nitromethyl derivative **3a-b**, in the presence of base (Scheme 1). By this method, the isoxazole **1a** was obtained in 22% yield (35% based on recovered **2**) after 3d at reflux in the presence of NEt₃ in ethanol. Using methyl nitroacetate **3b** the isoxazole **1b** was obtained in 19% yield, along with the isoxazole **1a** (7% yield) due to ester exchange, and 2-chloro-3-ethoxy-1,4-naphthoquinone **4a** (13% yield). To avoid the problem of ester exchange, we changed the solvent to MeOH but did not observe any formation of isoxazole after 3d at reflux (Table 1). In this case, we only isolated 2-chloro-3-methoxy-1,4-naphthoquinone **4b** (33% yield) - presumably due to the lower temperature of reflux.

We then decided to continue working on this new methodology in order to improve the low yields of naphtho[2,3-*d*]isoxazole-4,9-dione-3-carboxylates **1a-b**. An improved synthesis was accomplished, using diisopropylethylamine (2 eq.) as base, in the presence of molecular sieves.^{10a} In this case, the reaction

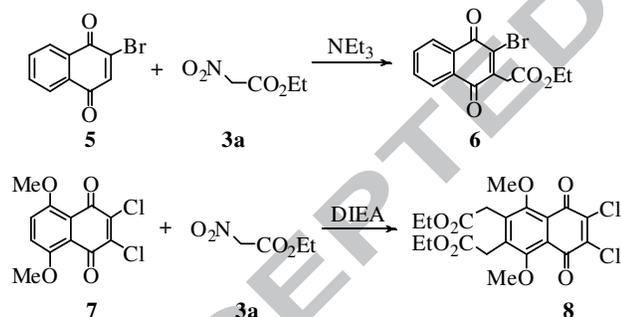
proceeded faster with no starting material being recovered; after 6.5 h we isolated isoxazole **1a** (33% yield), along with 2-chloro-3-ethoxy-1,4-naphthoquinone **4a**¹¹ (11% yield) formed by substitution of a Cl atom by the solvent. Using methyl nitroacetate **3b** the isoxazole **1b** was obtained in 33% yield, along with 2-chloro-3-ethoxy-1,4-naphthoquinone **4a** (12% yield).^{10a}



a EWG=CO₂Et; **b** EWG=CO₂Me; **c** EWG=SO₂Ph; **d** EWG=COPh

Scheme 1. Synthesis of naphtho[2,3-*d*]isoxazole-4,9-diones **1a-d**.

When 2-bromo-1,4-naphthoquinone **5** was used as starting material, naphthoquinone **6** (78% yield) was obtained from reaction with **3a**, after 6.5h at reflux in the presence of NEt₃ in ethanol (Scheme 2). Only after 29h at reflux, was the isoxazole **1a** obtained (13% yield), along with the naphthoquinone **6** (26% yield).^{12,13} The latter obviously arises from Michael addition of the nitronate anion at the least substituted quinone carbon atom followed by loss of the nitrite ion. Attack at the C-H carbon is presumably preferred because (i) this centre is less sterically hindered, and (ii) bromine stabilizes an adjacent anion better than does an H atom.



Scheme 2. Reactions of 2-bromo-1,4-naphthoquinone **5** and 2,3-dichloro-5,8-dimethoxy-1,4-naphthoquinone **7** with **3a**.

When we used 2,3-dichloro-5,8-dimethoxy-1,4-naphthoquinone **7** and **3a** as starting materials, after 1.5h at reflux in ethanol in the presence of 2 eq. of DIEA and molecular sieves, we isolated compound **8** in 56% yield (Scheme 2).¹⁴ In this case, no formation of isoxazole was observed, even after 30 h at reflux in the presence of NEt₃ (Table 1).

This method seems to be general for other nitromethyl derivatives, as it was also possible to obtain naphtho[2,3-*d*]isoxazole-4,9-diones with a sulfone **1c** and a ketone **1d** in position 3 (Scheme 1). When reaction of **2** was attempted with phenylsulfonylnitromethane **3c** or benzoylnitromethane **3d** in the presence of DIEA and ethanol, only 2-chloro-

3-ethoxy-1,4-naphthoquinone **4a**, from reaction of the quinone with the solvent, could be isolated (Table 1).^{10a} However, when we changed the solvent to acetonitrile, it was then possible to obtain the isoxazoles **1c** and **1d**, respectively (Table 1).^{10b} Isoxazole **1c** was only formed in the presence of NEt₃ (10% yield). In the presence of DIEA or K₂CO₃ a complex mixture of products was obtained. Isoxazole **1d** however was obtained using as bases DABCO (12% yield), NEt₃ (32% yield), DIEA (32% yield) or K₂CO₃ (23% yield). To try to improve the yield of **1d**, we decided to study the effect of using 2 equivalents of nitroacetate **3d**, however in the presence of NEt₃ in CH₃CN, we obtained a more complex mixture, and we could only isolate isoxazole **1d** in 14% yield.

Table 1. Reaction conditions used for the synthesis of compounds **1a-d**, **6** and **8**.

Starting materials	Solvent	Base	Reflux (h)	Product (Yield)	
2	3a	EtOH	DIEA	6.5	1a (33%) 4a (11%)
		EtOH	NEt ₃	6.5	6 (78%)
5	EtOH	NEt ₃	29.0	1a (13%) 6 (26%)	
		NEt ₃	29.0	6 (26%)	
7	EtOH	DIEA	1.5	8 (56%)	
		DIEA	30.0	8 (37%)	
2	3b	EtOH	DIEA	6.5	1b (33%) 4a (12%)
		MeOH	NEt ₃	72.0	4b (33%)
2	3c	EtOH	DIEA	96.0	4a (15%)
		CH ₃ CN	NEt ₃	4.0	1c (10%)
		CH ₃ CN	DIEA	2.0	???
		CH ₃ CN	K ₂ CO ₃	48.0	???
2	3d	EtOH	DIEA	24.0	4a (41%)
		CH ₃ CN	DABCO	6.0	1d (12%)
		CH ₃ CN	NEt ₃	5.0	1d (32%)
		CH ₃ CN	DIEA	4.5	1d (32%)
		CH ₃ CN	K ₂ CO ₃	5.0	1d (23%)

In all the above reactions, a complex mixture of products was obtained, and we could only isolate as the major products the products described in table 1.

Structural assignment of products **1** was based on spectroscopic data,¹⁶⁻¹⁷ which accorded with the literature.⁷ Confirmation of the isoxazole structure **1** came from the X-ray crystallographic analysis.¹⁸

Naphtho[2,3-*d*]isoxazole-4,9-diones **1a-d** and naphthoquinones **4a-b**, **6** and **8** were evaluated for their antifungal activity against various ATCC and PYCC reference strains of *Candida*.¹⁹ The MIC₅₀ values were calculated using probit analysis based on triplicate assays and are presented in Table 2. All compounds showed a reasonable level of antifungal activity at the µg/mL level, ranging from the lowest MIC₅₀ value of 0.2 µg/mL for compound **1a** against PYCC 2545 (*C. parapsilosis*) and PYCC 2418^T (*C. glabrata*) to the highest of 47.9 µg/mL for compound **4a** against ATCC 90028 (*C. albicans*).

Table 2. Determination of MIC₅₀ µg/mL (µM) for compounds **1a-d**, **4a-b**, **6** and **8**.

Compound	<i>C. albicans</i>	<i>C. albicans</i>	<i>C. krusei</i>	<i>C. parapsilosis</i>	<i>C. parapsilosis</i>	<i>C. glabrata</i>
	ATCC 90028	PYCC 3436 ^f	PYCC 3341	PYCC 2545	ATCC 22019	PYCC 2418 ^f
1a	3.1 (11.5)	0.5 (1.8)	0.6 (2.3)	0.2 (0.6)	0.5 (1.7)	0.2 (0.6)
1b	3.1 (12.2)	0.2 (0.7)	0.6 (2.4)	0.3 (1.3)	0.5 (1.8)	0.7 (2.6)
1c	19.2 (56.7)	0.8 (2.5)	3.3 (9.7)	0.5 (1.6)	2.1 (6.1)	0.5 (1.5)
1d	21.6 (71.2)	0.5 (1.6)	6.4 (21.2)	4.0 (13.2)	1.0 (3.3)	14.4 (47.6)
4a	47.9 (202.4)	2.3 (9.5)	0.9 (3.9)	11.4 (48.3)	9.6 (40.4)	0.9 (3.8)
4b	16.5 (73.9)	2.3 (10.4)	1.0 (4.6)	1.2 (5.3)	1.0 (4.7)	3.7 (16.7)
6	1.5 (4.5)	0.3 (0.9)	nd ^a	0.4 (1.1)	1.0 (3.2)	3.9 (12.0)
8	25.7 (56.0)	5.6 (12.2)	3.0 (6.5)	7.0 (15.2)	8.4 (18.4)	2.3 (5.1)
AmpB	1.1 (1.2)	0.5 (0.5)	0.9 (1.0)	0.4 (0.5)	0.4 (0.5)	0.3 (0.4)

a) Not determinate due to absence of yeast growth in all bioassays.

Inspection of the data in Table 2, allows the following observations to be made:

1. There was marked variability among the strains with regard to their susceptibilities to the various test compounds. This is particularly evident for the *C. albicans* ATCC 90028 and PYCC 3436T strains (e.g. compounds **1c**, **1d** and **4a**). Such variability suggests there are biological factor(s) affecting strain/species and test compound bioactivity.

2. Strain ATCC 90028 appeared to be the least sensitive, to almost all the compounds. Only compound **6**, with an MIC₅₀ of 1.5 µg/mL demonstrated antifungal activity equivalent to that of AmpB (Amphotericin B) for this strain. In addition, this compound also had notable activity against PYCC strains 2545 and 3436^f.

3. Only compounds **1a** and **1b** showed a level of activity equivalent to that of AmpB against strain ATCC 22019. Compound **1a** appeared to have the broadest antifungal activity, showing MIC₅₀ values at or below that of AmpB for all strains, except ATCC 90028. Compound **1b** was next in breadth of activity, with MIC₅₀ values at or below those of AmpB for four of the six strains. Compound **1c** demonstrated reasonable antifungal activity, with MIC₅₀ levels <1.0 µg/mL against PYCC strains, 2545, 3436^f and 2418^f.

4. The order of the antifungal activity in compounds **1** seems to depend on the nature of the EWG in position 3 and varies in the order ester > sulfone > ketone.

5. Compounds **1d**, **4a** and **4b**, also showed reasonable antifungal activities equivalent to that of AmpB against one strain, each. Compound **8**, although exhibiting fair antifungal activity at the µg/mL level against all strains, did not present any MIC₅₀ values at or below that of AmpB against any of the strains.

In summary, we describe a new methodology for the synthesis of isoxazoles **1** containing an EWG in position 3. Although the yields are lower than those described for the synthesis of isoxazole **1a** (lit. 55% yield),⁷ our procedure uses cleaner chemistry and only 1 equivalent of both commercial starting materials.

Also, our method is not restricted to the use of ethyl nitroacetate, but seems to be general for other nitromethyl derivatives. In addition, all the test compounds showed effective levels of antifungal activity at the µg/mL level. Importantly, **1a** and **1b** showed the broadest activity and were equivalent to or better than the standard antifungal drug Amphotericin B against five of the six strains examined. The observation that naphtho[2,3-*d*]isoxazole-4,9-dione-3-carboxylates **1a-b** are non-cytotoxic in human cellular lines⁹ strongly suggests that the naphtho[2,3-*d*]isoxazole-4,9-dione scaffold has the potential to be developed into novel and safe therapeutic antifungal agents. The mechanism for the formation of isoxazoles **1a-d** is under study.

Acknowledgment

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- a) nitromethyl derivative (2.2 mmol) and DIEA (4.4 mmol) were added to a solution of 2,3-

dichloro-1,4-naphthoquinone (2.2 mmol) in EtOH (50 ml) with molecular sieves. After reflux, under argon atmosphere, the solution was filtered and evaporated to dryness. The residue was submitted to flash chromatography (*n*-hexane/ethyl acetate 8:2); b) nitromethyl derivative (2.2 mmol) and base (4.4 mmol) were added to a solution of 2,3-dichloro-1,4-naphthoquinone (2.2 mmol) in CH₃CN (50 ml). After reflux, under argon atmosphere, the mixture was diluted with ethyl acetate and washed with H₂O (3?). The organic extract was dried and concentrated. The residue was submitted to flash chromatography (*n*-hexane/ethyl acetate 8:2).

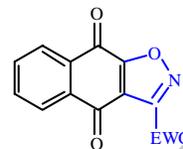
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12. Compound **6**: m.p. 122-124°C; IR (NaCl) 1721, 1674; ¹H (400 MHz, CDCl₃) 1.26 (3H, *t*, J=8.0 Hz, CH₃), 3.92 (2H, *s*, CH₂), 4.18 (2H, *q*, J=8.0 Hz, OCH₂), 7.76 (2H, *t*, J=4.0 Hz, ArH), 8.10-8.13 (1H, *m*, ArH), 8.15-8.18 (1H, *m*, ArH); ¹³C (100 MHz, CDCl₃) 14.1 (CH₃), 37.1 (CH₂), 61.6 (OCH₂), 127.3 (CHAr), 127.7 (CHAr), 131.1 (CAr), 131.2 (CAr), 134.2 (CHAr), 134.4 (CHAr), 141.2 (CAr), 144.7 (CAr), 168.1 (CO), 177.4 (CO), 181.1 (CO).
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14. Compound **8**: m.p. 134-135°C; IR (NaCl) 1723, 1661; ¹H (400 MHz, CDCl₃) 1.25 (3H, *t*, J=8.0 Hz, CH₃), 3.65 (2H, *s*, CH₂), 3.93 (3H, *s*, OMe), 4.15 (2H, *q*, J=8.0 Hz, OCH₂); ¹³C (100 MHz, CDCl₃) 14.1 (CH₃), 32.9 (CH₂), 61.6 (OCH₂), 62.0 (OCH₃), 124.4 (CAr), 136.7 (CAr), 141.6 (CAr), 153.2 (CAr), 169.0 (CO), 182.1 (CO).
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16. Compound **1c**: m.p. 190-191°C; IR (NaCl) 1716, 1675; ¹H (400 MHz, CDCl₃) 7.67 (2H, *t*, J=8.0 Hz, ArH), 7.78 (1H, *t*, J=8.0 Hz, ArH), 7.83-7.92 (2H, *m*, ArH), 8.24-8.30 (4H, *m*, ArH); ¹³C (100 MHz, CDCl₃) 118.9 (CAr), 127.7 (CHAr), 128.1 (CHAr), 129.5 (2 CHAr), 129.9 (2 CHAr), 131.5 (CAr), 133.0 (CAr), 134.3 (CHAr), 135.5 (CHAr), 135.8 (CHAr), 137.3 (CAr), 162.5 (CAr), 166.6 (CN), 172.3 (CO), 175.7 (CO). HMRS C₁₇H₁₀NO₅S (M+1) 340.02797, found 340.02847.
17. Compound **1d**: m.p. 124-125°C; IR (NaCl) 1689, 1589; ¹H (400 MHz, CDCl₃) 7.56 (2H, *t*, J=8.0 Hz, ArH), 7.69-7.73 (1H, *m*, ArH), 7.84-7.89 (2H, *m*, ArH), 8.08 (2H, *d*, J=8.0 Hz, ArH), 8.21-8.23 (1H, *m*, ArH), 8.30-8.32 (1H, *m*, ArH); ¹³C (100 MHz, CDCl₃) 121.2 (CAr), 127.7 (CHAr), 127.8 (CHAr), 129.0 (2 CHAr), 130.5 (2 CHAr), 132.0 (CAr), 133.3 (CAr), 134.7 (CHAr), 134.9 (CAr), 135.3 (CHAr), 135.5 (CHAr), 157.8 (CAr), 165.3 (CN), 177.0 (CO), 177.1 (CO), 188.9 (CO). HMRS C₁₈H₁₀NO₄ (M+1) 304.06098, found 304.06211.
18. Crystal Data for C₁₄H₉NO₅, *M_r* = 271.22, Triclinic space group P-1, *a* = 7.1485(3), *b* = 8.5516(2), *c* = 10.1860(5) Å, *β* = 79.315(2)°, *V* = 88.841(2) Å³, *Z* = 2, *D_c* = 1.515 g cm⁻³, *μ* = 0.117 mm⁻¹, *F*(000) = 280, pale yellow crystal 0.6 x 0.4 x 0.05 mm, *ρ*_{max} = 27.49?, 2704

unique data, 10685 measured (*R*_{int} = 0.0272), *R*₁ = 0.0363 and *wR*₂ = 0.0988 [*I* > 2σ(*I*)]. Supplementary data have been deposited with the CCDC deposition number CCDC674974.

19. Determination of MIC Levels: Antifungal activities of **1a-d**, **4a-b**, **6** and **8** and amphotericin B (AmpB; Sigma-Aldrich, Sigma A2411), were based on Minimal Inhibitory Concentrations for 50% cell death (MIC₅₀). Microtitre plate bioassays for determining the MIC₅₀ values were based on modified protocols outlined in the Clinical and Laboratory Standards Institute (CLSI), old National Committee for Clinical Laboratory Standards (NCCLS), document M27-A, National Committee for Clinical Laboratory Standards., Wayne, PA, USA. The compounds were first dissolved in dimethylsulfoxide (DMSO) (1 mg/mL) then further diluted 10-fold in SG (100 μg/mL, stock solution) (SG minimal medium: 6.7 mg/ml yeast nitrogen base w/o amino acids, 2% glucose). Next, 30 separate dilutions were made of each compound so that the microtitre plate wells had final concentrations of 97.5, 90, 80, 70, 60, 50, 40, 30, 20, 15, 10, 7.5, 5.0, 3.75, 2.5, 1.25, 1.0, 0.75, 0.5, 0.25, 0.125, 0.1, 0.075, 0.05, 0.0250, 0.0150, 0.0125, 0.01, 0.005 and 0.0025 μg/mL of each test compound or AmpB. The dilutions included respective volumes of stock solution and medium, plus 10 μl (approx. 5x10³ cells) of stock yeast culture to bring the final volume to 200 μl/well. Control wells included 20 μl DMSO up to 200 μl SG. All bioassay dilutions were done in triplicate. The plates were incubated at 30° C for 48 hours. Level of yeast cell reproduction for each concentration of the test compounds and AmpB was determined by optical density (OD) using a microtitre plate reader (Microplate Reader Model 680, Biorad) at 655nm. OD readings were converted to % cell reproduction (OD concentration/OD control). The mean of the triplicate readings was then determined. MIC₅₀ values were determined by probit analysis of % cell reproduction vs. concentration of test compounds or ampB using the statistical analysis program provided by SPSS (Chicago, IL, USA).

Reaction of Naphthoquinones with Substituted Nitromethanes. Facile Synthesis and antifungal activity of Naphtho[2,3-*d*]isoxazole-4,9-diones

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We report here a simple entry into naphtho[2,3-*d*]isoxazole-4,9-dione system containing a EWG in position 3. Antifungal activity of synthesised naphthoquinones was evaluated against ATCC and PYCC reference strains of *Candida*.