ORGANIC LETTERS

2009
Vol. 11, No. 14
2964−2967

Novel Thermal and Microwave-Assisted Facile Route to Naphthalen-2(1*H*)-ones via an Oxidative Alkoxylation-Ring-Opening Protocol

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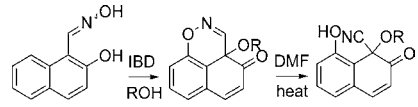
Received April 19, 2009

ABSTRACT



Several novel 1,1-disubstituted-8-hydroxynaphthalen-2(1*H*)-ones have been efficiently synthesized via a two-step sequence from 2-hydroxy-1-naphthaldehyde oxime. The methodology involves oxidative ring closure and alkoxylation to 3a-alkoxynaphtho[1,8-*de*][1,2]oxazin-4(3a*H*)-ones, followed by thermal ring-opening. Both thermal and microwave irradiation conditions were used. A novel one-pot reaction of oxime to 8-isopropoxynaphthalene-1,7-diol using microwave irradiation is also reported.

Naphthalen-2(1*H*)-ones are an important class of pharmacologically active compounds. 1-Hydroxy-1,6-dimethylnaphthalen-2(1*H*)-ones **1**−**3** belong to a group of phytoalexines, produced by the cotton plant *Gossypium hirsutum* when infected by bacteria.[1a] The second member exhibits in vitro chemotactic activity toward human polymorphonuclear leukocytes.[1b] Non-natural compounds such as **4** are HIV-1 reverse transcriptase inhibitors,[1c] **5** are inhibitors of genotype 1 hepatitis C virus (HCV) polymerase,[1d,e] whereas **6** exhibit prolyl hydroxylase inhibitory activity.[1f] A large number of synthetic routes to 1,1-disubstituted naphthalen-2(1*H*)-ones have been described. In particular, attention has been paid to the synthesis of 1,1-difluoronaphthalen-2(1*H*)-one, useful as a synthetic intermediate and a tool for elucidating biological processes. The compound is synthesized by fluorination of 2-naphthol,[2a−h] 2-methoxynaphthalene,[3f,g] 1-alkoxy-2-fluoronaphthalenes, or 2-(*N*-acetylamino)naphthalene.[2a,b] Other 1,1-disubstituted naphthalen-2(1*H*)-ones have been synthesized by amination of sodium 1-methylnaphthalen-2-olate,[2i] methylation of 1-methyl-2-naphthol,[2j] oxidation of 4-isopropyl-7-methoxy-1,6-dimethyl-2-naphthol,[2k] reaction of sodium naphthalen-2-olate with alkyl halides over supported hexamethylphosphoric

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10.1021/ol9008574 CCC: $40.75
Published on Web 06/24/2009

triamide,[2l] chlorination of 2-naphthol and decomposition of 1,1,3,4-tetrachlorotetralin-2-one,[2m] oxidation of 1,1-dimethylnaphthalene-2(1*H*)-thione,[2n] radical-mediated oxidative cyclization of 1-(3,5-dimethoxyphenyl)hex-1-ene-3,5-diones,[2o] oxidation of 1,1-dimethyl-1,2-dihydronaphthalen-2-ol,[2p] and Claisen rearrangement followed by ring-closing metathesis of 1-allyl-2-(allyloxy)naphthalenes.[2q] Among the plethora of microwave-assisted transformations, oxidation with hypervalent iodine reagents stands out as the most common green chemistry protocol that employs solid-supports and benign reaction media.[3a] Iodobenzene diacetate has been used in reactions with solid-supports,[3b−e] with water as solvent,[3f−h] without solvent,[3i−l] and with common organic solvents[3m−q] (Figure 1).

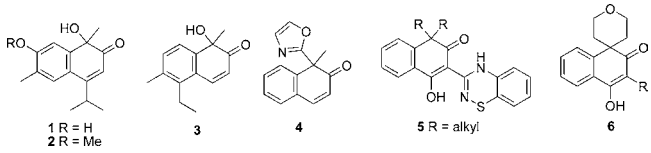
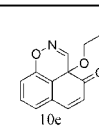
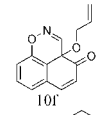
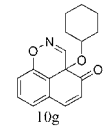


Figure 1. Pharmacologically active naphthalen-2(1*H*)-ones.

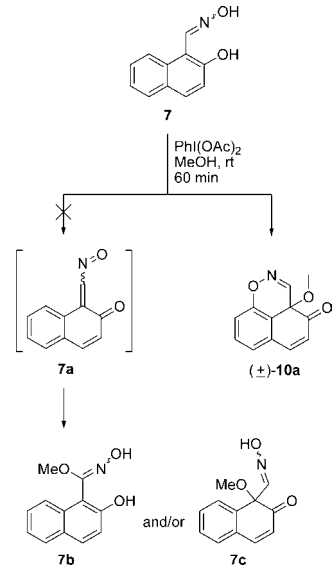
Herein, we report a novel two-step synthesis of 1,1-disubstituted-8-hydroxynaphthalen-2(1*H*)-ones (1-alkoxy-8-hydroxy-2-oxo-1,2-dihydronaphthalene-1-carbonitriles) **11a**−**g** (Scheme 2, Table 2) from 2-hydroxy-1-naphthaldehyde oxime **7** via oxidative ring closure and alkoxylation to 3a-alkoxynaphtho[1,8-*de*][1,2]oxazin-4(3a*H*)-ones **10a**−**g** (Table 1), followed by thermal ring-opening. Both conventional and microwave conditions were used and the results are compared. This synthesis was inspired by an unexpected observation as shown in Scheme 1. On the basis of our previous observation that 2-hydroxy-1-naphthaldehyde oxime **7** undergoes a one-pot *o*- and *peri*-oxidative cyclization with lead(IV) acetate to give isomeric naphtho[1,2-*d*]isoxazole 2-oxide and naphtho[1,8-*de*][1,2]-oxazine via a common *o*-naphthoquinone nitrosomethide intermediate **7a**,[4] we envisaged that the oxidation of compound **7** with iodobenzene diacetate in methanol would lead to reactive intermediate **7a**, followed by fast Michael addition of methanol to give **7b** and/or **7c**. When compound **7** was treated with 2

Table 1. Examples of Alkoxynaphthooxazin-4(3a*H*)-ones **10** Prepared (Scheme 2)[a]

entry	product	time (min) (T)/(MW)	yield (%)[b] (T)/(MW)	entry	product	time (min) (T)/(MW)	yield (%)[b] (T)/(MW)
1	 10a	60/4	65/79	5	 10e	60/6	55/64
2	 10b	60/4	63/69				
3	 10c	40/4	59/70	6	 10f	60/4	53/71
4	 10d	70/9	56/62	7	 10g	70/8	57/62

[a] Representative procedure. Thermally (T): compound **7** (1.07 mmol), IBD (2.17 mmol), and appropriate alcohol (15 mL) were stirred at 22 °C for the indicated time. Microwave-irradiation (MW): compound **7** (1.07 mmol), IBD (2.17 mmol), and appropriate alcohol (15 mL) were irradiated at a ceiling temperature of 40 °C and a maximum power level of 100 W for the indicated time. [b] Isolated yields after column chromatography.

Scheme 1



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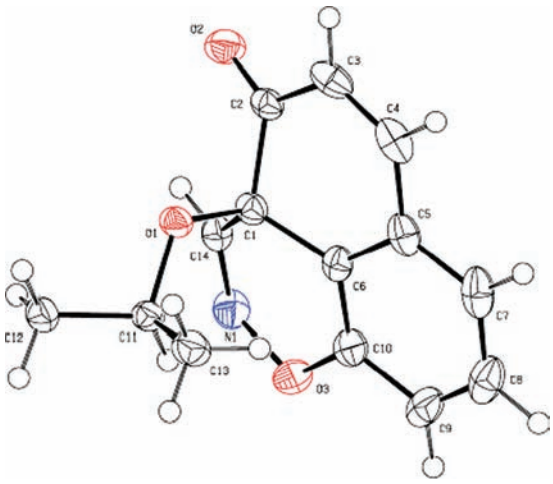
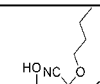
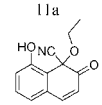
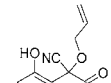
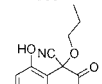
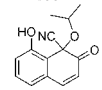


Figure 2. X-ray molecular structure of **10d**, with atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

equiv of iodobenzene diacetate in methanol, the ^{1}H and ^{13}C NMR and mass spectra of the compound isolated did not account for the expected compounds **7b** or **7c** or any of their possible oxidation products (Scheme 1). Structure **10a** (Scheme 1, Table 1, entry 1) was tentatively assigned to the product and later confirmed by comparison with the product from the reaction of compound **7** with 2 equiv of iodobenzene diacetate in *i*-propanol (70 min reaction time). The structure of this product **10d** (Table 1, entry 4) was determined by single crystal X-ray crystallographic analysis (Figure 2). The X-ray structure features a chiral center on the C-atom C1. The compound crystallized in the centrosymmetric space group $P\bar{1}$, hence both enantiomers are present in the structure. No classic hydrogen bonds are observed. Stacking interactions occur between the C5−C10 aromatic ring and the same ring of a symmetry-equivalent molecule (3.8 Å between the ring centroids).

The reaction of compound **7** with iodobenzene diacetate was repeated in the presence of other alcohols (Table 1). Attempts to optimize the yields of compounds **10a**−**g** by varying reaction time and the stoichiometry of reagents resulted in the conclusion that 2 equiv of iodobenzene diacetate was optimum for all the alcohols whereas reaction times varied from 40 to 70 min (Table 1). To reduce reaction time and improve on the yields of compounds **10a**−**g**, the reaction of compound **7** with 2 equiv of iodobenzene diacetate in the appropriate alcohol was repeated using microwave irradiation at 40 °C. Optimum reaction times for these reactions were found to be 4−9 min (Table 1). The corresponding products **10a**−**g** were isolated in 62−79% yields. In Table 1, a comparison of reaction times and yields of the conventional heating method and the microwave irradiation method is given. The microwave method is superior because it reduces the conventional reaction time from a maximum 70 to 8 min and the conventional minimum time of 30 to 4 min. There is a moderate increase in the yield of products by the microwave method ranging from 6 to 18%.

Table 2. Examples of Naphthalen-2(1*H*)-ones **11** Prepared (Scheme 2)[a]

entry	product	time (min) (T)/(MW)	yield (%)[b] (T)/(MW)	entry	product	time (min) (T)/(MW)	yield (%)[b] (T)/(MW)
1	 **11a**	30/4	82/88	5	 **11e**	30/4	78/84
2	 **11b**	30/4	78/86	6	 **11f**	30/4	78/84
3	 **11c**	30/4	78/82	7	 **11g**	30/4	78/86
4	 **11d**	30/4	82/80				

[a] Representative procedure. Thermally (T): appropriate compound **10** (0.35 mmol) and DMF (5 mL) were heated at 120 °C for the indicated time. Microwave-irradiation (MW): appropriate compound **10** (0.35 mmol) and DMF (5 mL) were irradiated at a ceiling temperature of 40 °C and a maximum power level of 150 W for the indicated time. [b] Isolated yields after column chromatography.

In our previous work concerning the synthesis of 4-hydroxynaphtho[1,8-*de*][1,2]oxazine, we demonstrated that upon heating this compound in DMF at 120 °C, ring-opening occurred to give 2,8-dihydroxynaphthalene-1-carbonitrile.[4] Overall this reaction is important because it implies an intramolecular nuclear hydroxylation. Hydroxylation and oxygennation are important biological processes.[5a,b] We therefore thought that a similar ring-opening of compounds **10a**−**g** would occur. Thus, heating compounds **10a**−**g** in DMF at 120 °C for 30 min resulted in ring-opening of these compounds to give the corresponding 1,1-disubstituted-8-hydroxynaphthalen-2(1*H*)-ones **11a**−**g**, in 77−82% yields (Table 2). Application of microwave irradiation to these reactions required the same temperature but reaction time was drastically reduced to 4 min. A comparison of the yields of compounds **11a**−**g** by the conventional and microwave methods establishes that the yields using microwave irradiation show a small increase of 4−8% and, remarkably, a 2% decrease in the yield of compound **11d** (Table 2).

A plausible mechanistic explanation, for the overall transformation of **7** to the oxidatively alkoxylated naphthooxazinones **10a**−**g** and then thermal ring-opening to the corresponding alkoxylated naphthalenone-carbonitriles **11a**−**g**, is shown in Scheme 2. To establish that the first step of the reaction gives the *peri*-oxidative cyclization intermediate **8**, compound **7** was treated with 1 equiv of iodobenzene diacetate in methanol to afford, after chromatographic separation, compound **8** and starting material **7** in 60 and 32% yields, respectively. Moreover, treating compound **7** with 2 equiv of iodobenzene diacetate in *t*-butanol afforded only compound **8** in 80% yield. It is reasonable to assume that attack of *t*-butanol on **9** is sterically

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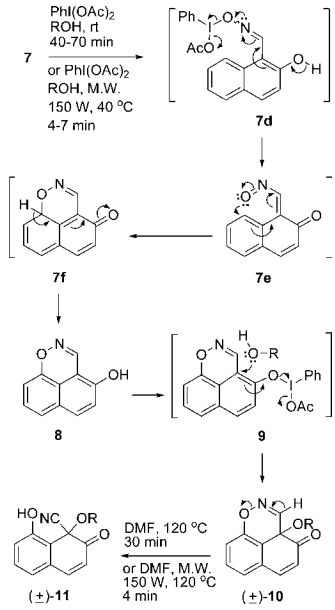
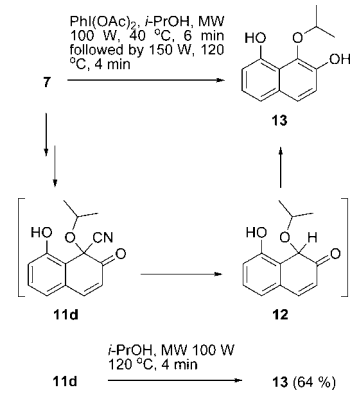
Scheme 2. Proposed Mechanism for the Formation of **10** and **11**



Scheme 3. Proposed Mechanism for the Formation of **13** from **7**



impeded and the latter hydrolyses back to **8** upon aqueous workup. Furthermore, we found out that oxidation of compound **8** with 1 equiv of iodobenzene diacetate in methanol gives the expected 3a-methoxynaphthooxazin-4(3a*H*)-one **10a** in 75% yield. We therefore unequivocally established that compound **8** is an intermediate in this reaction. The formation of compound **8** from oxime **7** has been previously described using lead(IV) tetraacetate.[4] Herein we propose a similar mechanistic pathway whereby the organoiodo intermediate **7d** collapses to the reactive *o*-naphthoquinone nitrosomethide intermediate **7e** that undergoes intramolecular *peri*-cyclization to intermediate naphthooxazinone **7f**. The latter then tautomerises/aromatizes to naphthooxazine **8**. In the next step, we propose that organoiodo intermediate **9** triggers nucleophilic attack by the alcohol onto strongly electrophilic C-3a atom that leads to **10**. There is substantial evidence for this type of reaction in the literature such as, for example, the iodobenzene diacetate oxidative alkoxylation of 2,3-disubstituted indoles to 3-alkoxyindolenines, of 4-alkyl- and 4-alkoxyphenols to the corresponding 4-alkyl-4-methoxy- and 4-alkoxy-4-methoxy-cyclohexadienones,[7] as well as the oxidative cyclization of 2′-alkenyl-substituted *p*-phenyl phenols to spiro-annulated 2,5-cyclohexadienones.[8] The ring-opening step of this reaction sequence employs DMF as the solvent at a temperature of 120 °C that causes the cleavage of the O−N bond of compound **10** with concomitant prototropic isomerization to naphthalenone **11**. A similar type of ring-opening was substantiated in our previous work.[4]

We also examined the possibility of converting, in a one-pot reaction, compound **7** to alkoxynaphthalenone-carbonitriles **11** with 2 equiv of iodobenzene diacetate in alcoholic solutions using microwave irradiation. The reaction took place in *i*-propanol using 100 W irradiation at 40 °C for 6 min followed by 150 W irradiation at 120 °C for 4 min. To our surprise, the product we isolated was identified as 8-isopropoxynaphthalene-1,7-diol **13** (Scheme 3). A mechanism for this result is tentatively proposed. The first two steps of the reaction correspond to those of Scheme 2 and lead to compound **11d**. The *i*-propanol containing water probably hydrolyses the nitrile **11d** to the ketoacid[9] which could be decarboxylated to **12**. Intermediate **12** may then tautomerise/aromatize to **13**. Partial evidence for this mechanism was obtained by a further experiment where **11d** was converted to **13** using 150 W microwave irradiation at 120 °C for 4 min.

In conclusion, we have designed a new, convenient and high yielding synthetic approach to 1,1-disubstituted-8-hydroxynaphthalen-2(1*H*)-ones from 2-hydroxy-1-naphthaldehyde oxime in the presence of alcohols. The reaction occurs in two-steps, a one-pot oxidative ring closure to naphtho[1,8-*de*][1,2]oxazin-4-ol and then alkoxylation to 3a-alkoxynaphtho[1,8-*de*][1,2]oxazin-4(3a*H*)-ones, followed by thermal ring-opening. Each reaction step was performed comparatively under thermal and microwave conditions. The advantage of microwave irradiation is shorter reaction time and higher yields (with one exception) of products. Furthermore, we obtained a novel one-pot conversion of 2-hydroxy-1-naphthaldehyde oxime to 8-isopropoxynaphthalene-1,7-diol in *i*-propanol by a two-stage microwave irradiation.

Acknowledgment. Financial support from the Socrates/Erasmus Exchange Programme between the University of Ioannina and Katholieke Universiteit Leuven (grant to C.D.) is gratefully acknowledged.

Supporting Information Available: Detailed synthetic procedures, product characterization, ^{1}H NMR, ^{13}C NMR and MS spectra of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9008574

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(9) A referee has kindly suggested that alternatively, hydrolysis of the cyano group of **11d** to the ketoacid may occur via the hydrated form of the keto group acting intramolecularly as a nucleophile.
(10) CCDC-725437 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44−1223−336033; or deposit@ccdc.cam.uk).