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Oxidative Amidation in the Naphthalene Series

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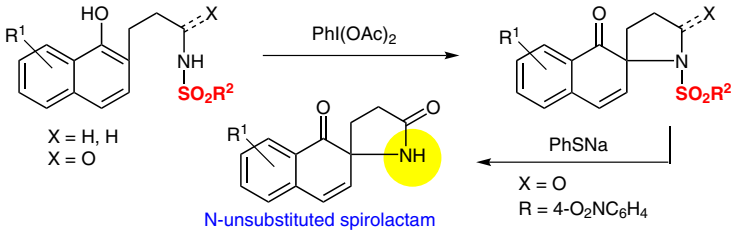

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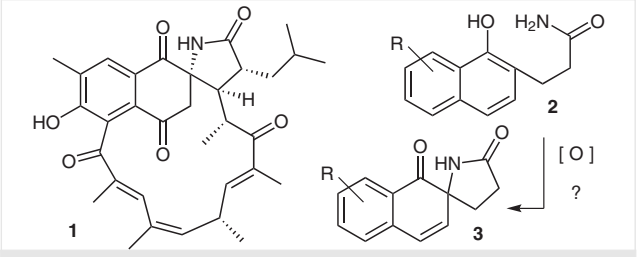
Abstract The successful oxidative spirocyclization of 1- or 2-naphtholic sulfonamides extends oxidative amidation methods to the naphthalene series. A method to prepare N-unsubstituted spirolactam derivatives of 1-naphthol is also presented.

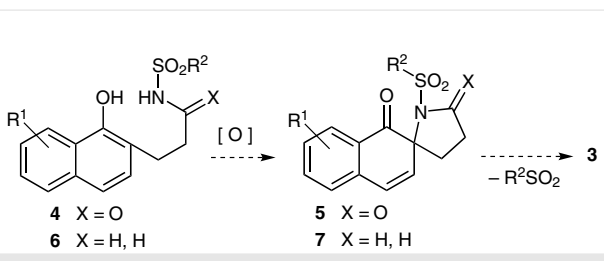
Key words heterocycles, iodine, phenols, spiro compounds, sulfonamides

The recent discovery of the marine natural product, ansalactam A, **1** (Scheme 1),[1] has rekindled our interest in a yet unresolved problem in phenolic oxidative amidation chemistry:[2] the assembly of N-unsubstituted spirolactams **3** by oxidative cyclization of primary phenolic carboxamides **2**, or analogues thereof. This transformation remains elusive because, as first detailed by Kita,[3] oxidative activation of phenolic amides (e.g., with a hypervalent iodine reagent)[4] does not lead to spirolactams, but to spirolactones. Thus, one may anticipate that attempted oxidative cyclization of **2** would not produce **3**, but rather lactone **17** (see Figure 1).[5] Particular *N*-alkyl variants of **3** are available by oxidative cyclization of phenolic oxazolines in the presence of (diacetoxyiodo)benzene (DIB).[6] However, this technique is unsatisfactory for the assembly of N-unsubstituted spirolactams, which have thus remained beyond the scope of oxidative amidation chemistry.

On the other hand, it is well established that phenolic sulfonamides and phosphoramides undergo efficient spirocyclization upon reaction with DIB.[7] This induced us to study the heretofore unknown oxidative conversion of an *N*-acylsulfonamide **4** into spirolactam **5** (Scheme 2). It seemed plausible that if the reaction were to succeed with a substrate that incorporates a sulfonyl group that might be cleavable under mild conditions,[8] the initially formed **5** could be readily elaborated to the desired **3**. One complication with this surmise was that, in the past, analogous oxidative amidations had been achieved only with phenolic substrates: similar transformations in the naphthol series are unknown.[9] Therefore, it seemed prudent first to ascertain the feasibility of oxidative amidation reactions with naphthol substrates. To that end, the oxidative conversion of naphtholic sulfonamides **6**[10] into spirocycles **7** was investigated. Such oxidative transformations were indeed found to occur efficiently. More significantly, *N*-acylsulfonamides **4** were determined to be good substrates for oxidative conversion into **5**. This enabled the development of a method for the assembly of lactams **3** based on the logic presented in Scheme 2.



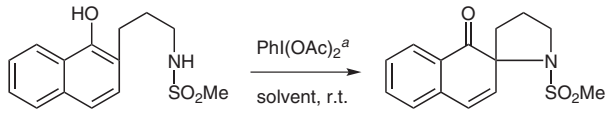
Scheme 1 Ansalactam A and a possible route to lactams **3**



Scheme 2 Plausible avenues to spirolactams **3**

Initial experiments aiming to establish the feasibility of the desired transformation, and the best solvent for it, focused on the DIB-mediated oxidative cyclization of a test substrate **6**, wherein R^1 = H and R^2 = Me. As seen in Table 1, highest yields were obtained by operating in neat trifluoroacetic acid (TFA), as in the case of phenolic sulfonamides.[7]

Table 1 Oxidative Cyclization of a Mesylamide of Type **6**[a]



Entry	Solvent	Yield (%)[b]
a	CF_3CH_2OH	20
b	$(CF_3)_2CHOH$	28
c	CH_2Cl_2	14
d	$CHCl_3$	12
e	CH_2Cl_2 + TFA (1.1 equiv)	30
f	$CHCl_3$ + TFA (1.1 equiv)	18
g	CH_3COOH	4
h	CF_3COOH	65

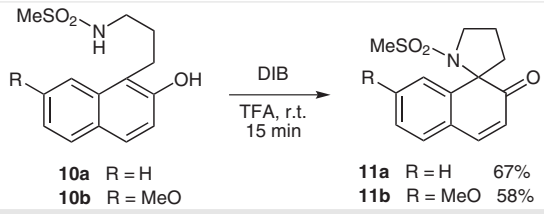
[a] Performed with DIB (1.1 equiv), 10–15 min.
[b] Yield of chromatographically purified product.

Treatment of substrates **8**[11] with DIB in TFA, under the same conditions induced cyclization to spirocycles **9** in generally good to excellent yield (Table 2), with the exception of **8e** and **8g**, which furnished product **9** in only 45 and 55% yield respectively, and **8i**, which gave no spirocyclic product.

The failure of **8i** to afford **9** may be due to the poor stability of the product under the acidic conditions of the reaction. However, no effort was made to identify the byproducts obtained from **8i**.

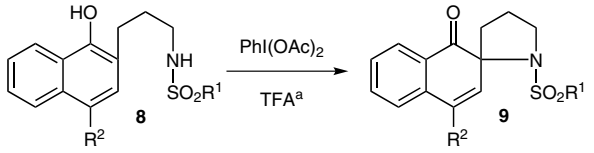
The 2-naphthol-based sulfonamides **10**[11] were easily converted into **11** in a similar manner (Scheme 3). These results convincingly extend the scope of oxidative cyclization of sulfonamides to the naphtholic series.

A more significant issue, the construction of lactams **3** according to Scheme 1, was addressed by exploring the oxidative cyclization of *N*-acyl-sulfonamides **14**. These were prepared by EDCI-mediated coupling of acid **12** with appropriate sulfonamides, followed by release of the *O*-TBS group (Scheme 4). Whereas the coupling step proceeded rather uneventfully, the desilylation of compounds **13** proved to be a delicate operation that had to be followed closely, because of the tendency of products **14** to cyclize to lactones **18** (Figure 1). The problem was especially acute with substrate **13c**, probably as a consequence of the more pronounced nucleofugal properties of 4-nitrosulfonamide relative to, for example, methanesulfonamide. In that connection, it is worthy of note that desilylation of **13c** with only 1.1 equivalents of tetrabutylammonium fluoride (TBAF) yielded mostly **18**, but successful deprotection was achieved when the reaction was carried out with 2.2 equivalents. Under such conditions, the anticipated product **14c** was actually obtained in the form of the bis-tetrabutylammonium salt.



Scheme 3 Oxidative cyclization of 2-naphtholic sulfonamides

Table 2 Oxidative Cyclization of 1-Naphtholic Sulfonamides[a]



Entry	R^1	R^2	Yield (%)[b]
a	4-MeC_6H_4	H	74
b	$4\text{-O}_2NC_6H_4$	H	75
c	4-MeOC_6H_4	H	80
d	$PhCH_2$	H	96
e	CF_3CH_2	H	45
f	Me	H	65
g	Me	Ph	55
h	Me	Br	83
i	Me	MeO	–

[a] Performed with DIB (1.1 equiv), r.t., 10–15 min.
[b] Yield of chromatographically purified product.

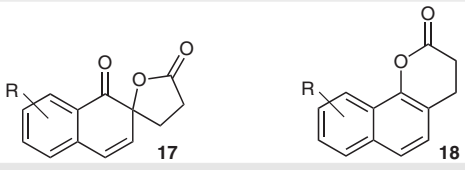
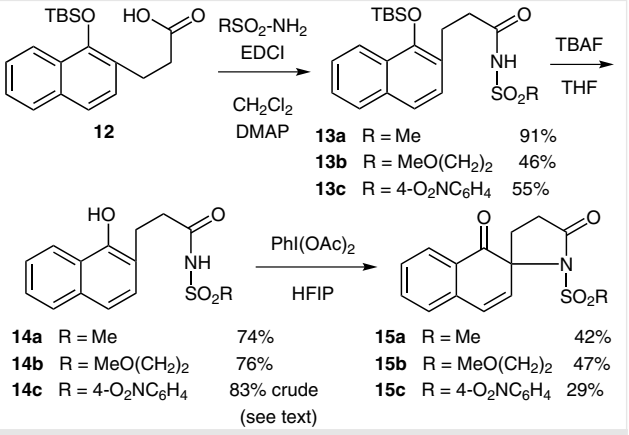


Figure 1 Compound **17**: spirolactone anticipated to result upon attempted oxidative cyclization of amides **2**. Lactone **18**: byproduct obtained upon desilylation of *N*-acylsulfonamides **13**

Attempts to restore the neutral form of the molecule by mild acidification resulted in cyclization to **18**. We note that N-deprotonation of acylsulfonamides is well known to retard or suppresses the nucleophilic displacement of the sulfonamide segment.[12]



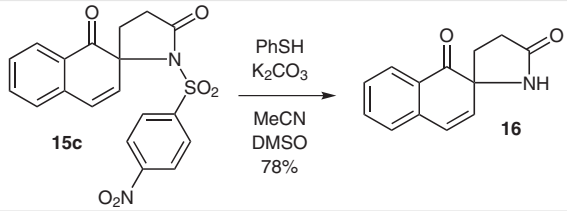
Scheme 4 Preparation and oxidative cyclization of 1-naphthol-derived *N*-acylsulfonamides **14**

Acylsulfonamides **14** proved to be rather sensitive and could not be purified to homogeneity. Acceptable losses were incurred during a quick chromatographic purification of compounds **14a** and **14b**. In contrast, the bis-tetrabutylammonium salt of compound **14c** was too sensitive and did not withstand purification, even by crystallization. Furthermore, substances **14** possessed limited shelf life. They could be stored at –20 °C and under argon for some days, but even under these conditions, degradation was apparent by NMR analysis after about ten days.

The oxidative cyclization of **14** could not be carried out in neat TFA (the medium of choice for the cyclization of sulfonamides **8** and **10**), because dissolution of the compounds in that solvent triggered rapid formation of lactones **18**. Fortunately, successful oxidative cyclization to spirolactams **15** (Scheme 4) was achieved in moderate yield by rapid addition of a solution of **14** in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)[13] into a solution of DIB in TFA, at room temperature. Whereas partially purified **14a** and **14b** were used in this step, the bis-Bu_4N^+ salt of **14c** was employed in crude form (recall, poor stability precluded purification). The resultant spirocycles **15** were considerably sturdier than their precursors **14**.

Chromatographic purification was achieved without difficulty, and the compounds thus obtained seemed to be quite stable for prolonged periods of time at room temperature. As a precaution, however, they were stored as solids at –20 °C (Ar).

Nitrosulfonamide **15c** provided the proof of principle for the feasibility of the transformation depicted in Scheme 1. Thus, reaction of crude **15c** with PhSH and K_2CO_3 in MeCN–DMSO[8] afforded the target spirolactam **16** in 78% yield (Scheme 5).[14]



Scheme 5 N-Deblocking of nitrosulfonamide **15c**

In summary, the oxidative *ortho*-cyclization of 1- and 2-naphtholic sulfonamides occurs in synthetically useful yields. A new method for the preparation of N-unsubstituted spirolactams of the type found in some recently discovered alkaloids has been demonstrated, although the technique requires additional refinement. Relevant advances will be the subject of future disclosures from these laboratories.

Acknowledgment

We thank, our former co-worker, Ms. Doris Tang, for carrying out preliminary experiments on the cyclization of phenolic (not naphthol-based) *N*-acylsulfonamides, and the University of British Columbia, the Canada Research Chair Program, NSERC, CFI and BCKDF for support of our research.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379960.

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(11) These materials were prepared from the corresponding naphthols by O-allylation, Claisen rearrangement, and further elaboration of the resultant *ortho*-allylnaphthols in a conventional fashion, as detailed in the Supporting Information.
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(14) **1′-Tosyl-1*H*-spiro[naphthalene-2,2′-pyrrolidin]-1-one (9a); Typical Procedure:** The preparation of this compound illustrates the general procedure for the cyclization of substrates **8**. A solution of sulfonamide **8a** (20 mg, 0.4 mmol, 1.0 equiv) in TFA (0.7 mL) was slowly added at room temperature over a period of 2 min to a solution of DIB (0.44 mmol, 1.1 equiv) in TFA (0.5 mL) so that the final concentration was 0.3 M. Upon completion of the reaction (TLC, 10 min), the mixture was evaporated to dryness. Chromatographic purification of the residue (silica gel; EtOAc–hexanes, 1:3) provided **9a** (15 mg, 74%) as a yellow solid; mp 115–117 °C. IR: 1686 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.2 Hz, 1 H), 7.72 (d, *J* = 8.3 Hz, 2 H), 7.58 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.36 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.29–7.24 (m, 3 H), 6.59 (d, *J* = 9.9 Hz, 1 H), 6.27 (d, *J* = 9.8 Hz, 1 H), 3.64–3.60 (m, 2 H), 2.42 (s, 3 H), 2.26–2.03 (m, 2 H), 2.02–1.95 (m, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 198.4, 143.2, 137.4, 137.1, 136.6, 134.8, 129.3, 128.7, 128.0, 127.7, 127.6, 127.5, 124.5, 70.9, 48.9, 39.5, 23.0, 21.6. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{19}NO_3SNa$: 376.0983; found: 376.0983.
1′-(Methylsulfonyl)-2*H*-spiro[naphthalene-1,2′-pyrrolidin]-2-one (11a): The cyclization of 2-naphthol-derived substrates **10** was achieved by the same procedure detailed above. Thus, **10a** (25 mg) afforded **11a** (16 mg, 67%) after column chromatography (EtOAc–hexane, 2:3) as a white solid; mp 116–118 °C. IR: 1672 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.8 Hz, 1 H), 7.47–7.42 (m, 2 H), 7.32–7.31 (m, 2 H), 6.17 (d, *J* = 9.9 Hz, 1 H), 3.96 (dt, *J* = 8.7, 6.2 Hz, 1 H), 3.76 (dt, *J* = 8.7, 7.0 Hz, 1 H), 3.10 (s, 3 H), 2.38 (dt, *J* = 12.0, 7.1 Hz, 1 H), 2.17 (quintet, *J* = 6.6 Hz, 2 H), 2.07–1.98 (m, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 200.5, 146.5, 146.0, 130.6, 129.8, 128.5, 127.7, 125.8, 123.7, 75.8, 49.9, 44.2, 40.0, 22.8. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{15}NO_3SNa$: 300.0670; found: 300.0665.
1′-(Methylsulfonyl)-1*H*-spiro[naphthalene-2,2′-pyrrolidine]-1,5′-dione (15a): A solution of **14a** (19 mg, 0.1 mmol, 1.0 equiv) in HFIP (2.0 mL) was added to a solution containing DIB (0.11 mmol, 1.1 equiv) in TFA (0.23 mL) at room temperature so that the final concentration was 0.05 M. Upon completion of the reaction (TLC, 5–12 min), the reaction mixture was evaporated to dryness. Chromatography of the residue (silica gel; EtOAc–hexane, 3:7) gave **15a** (8 mg, 42%) as a white solid; mp 169–171 °C. IR: 1737, 1686 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.7 Hz, 1 H), 7.64 (t, *J* = 7.5 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.30–7.27 (m, 1 H), 6.61 (d, *J* = 9.8 Hz, 1 H), 6.43 (d, *J* = 9.8 Hz, 1 H), 3.38 (s, 3 H), 2.84–2.58 (m, 2 H), 2.33 (ddd, *J* = 13.4, 9.4, 3.9 Hz, 1 H), 2.20–2.09 (m, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 197.1, 174.7, 137.5, 135.8, 135.3, 128.6, 128.1, 127.9, 127.4, 124.7, 71.4, 41.6, 29.8, 28.9. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{13}NO_4SNa$: 314.0463; found: 314.0468.
1*H*-spiro[naphthalene-2,2′-pyrrolidine]-1,5′-dione (16): A solution of sulfonamide **15c** (20 mg, 0.05 mmol, 1.0 equiv) in MeCN (1.0 mL) was added at room temperature to a solution of PhSH (16 mg, 15 µL, 150 µmol, 3.0 equiv) in MeCN (0.4 mL) containing suspended K_2CO_3 (28 mg, 0.2 mmol, 4.0 equiv). DMSO (0.1 mL) was then added to the reaction mixture and stirring was continued at room temperature for 2 h, after which time TLC showed that the reaction was complete. The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and evaporated. The residue was dried under high vacuum and purified by flash column chromatography (silica gel; EtOAc–hexane, 3:4) to provide **16** (8 mg, 78%) as a white solid; mp 131–133 °C. IR: 3430–3100 (br), 1698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.6 Hz, 1 H), 7.62 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.41 (td, *J* = 7.7, 0.7 Hz, 1 H), 7.30–7.29 (m, 1 H), 6.62 (d, *J* = 9.8 Hz, 1 H), 6.18 (d, *J* = 9.8 Hz, 1 H), 5.57 (br s, 1 H), 2.71–2.59 (m, 1 H), 2.46–2.31 (m, 2 H), 2.17–2.05 (m, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 199.4, 178.8, 137.1, 135.3 (2C), 128.7, 127.9, 127.7 (2C), 127.0, 65.0, 32.2, 28.2. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{11}NO_2$: 236.0687; found: 236.0687.