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Oxidative Spirocyclization of β-Furyl Amides for the Assembly of Spiro-γ-butenolide-γ-butyrolactones

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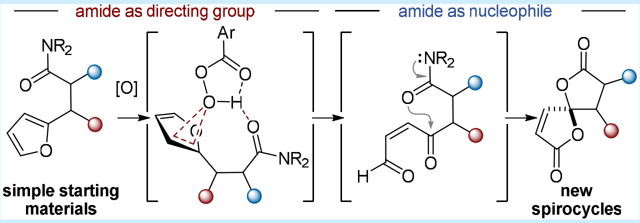

ABSTRACT: The synthesis of heretofore unknown γ-spirobutenolides has been achieved via an *m*-CPBA-mediated oxidation of β-furyl amides. The reaction employs a tethered amide, ostensibly a poorly reactive carbonyl, as a nontraditional nucleophile resulting in spirolactone formation and concurrent amide cleavage. The transformation exhibits functional group tolerance and compatibility with complex compounds. *In situ* ^{1}H NMR spectroscopic studies reveal the identities of key intermediates in the oxidation−spirolactonization−oxidation cascade, suggesting a plausible mechanistic pathway. The distinct diastereofaces of the electrophilic butenolide product may be used for diastereoselective cycloaddition and conjugate addition reactions.

Spirobutenolides and spirobutyrolactones represent common motifs in both natural products and bioactive compounds (Scheme 1a).[1−3] Surprisingly, the structure resulting from the fusion of these two substructures—a spiro-γ-butenolide-γ-butyrolactone (Scheme 1b)—has remained underexplored, with the exception of several benzo-fused examples.[4,5] Given the growing interest in spirocycles for drug discovery[6,7] and agricultural applications,[8] it was with excitement that we observed the formation of spiro-γ-butenolide-γ-butyrolactone **2a** upon attempted Baeyer−Villager oxidation of aryl ketone **1a** (Scheme 1b). Although furan oxidation by peracids is well established,[9,10] efficient engagement of the amide was not initially anticipated. This transformation bears some resemblance to the *m*-CPBA-mediated synthesis of spirobutenolide substructures previously reported by Robertson and co-workers,[11] where a tethered alcohol was used as the nucleophile.

Recognizing the possible utility of the observed transformation and the potential advantages of β-furyl amides as synthetic precursors to spirobutenolide substructures, not the least of which are the former's stability and potential to be carried through numerous synthetic manipulations, we herein disclose a method developed based upon this original, serendipitous result (Scheme 1c). A brief screen of reaction conditions revealed 2.5 equiv of *meta*-chloroperbenzoic acid (*m*-CPBA) were sufficient, rather than the 8.0 equiv used in the initial discovery. With that modification, the scope of the discovered transformation was explored (Scheme 2).

Several amides were tested as nucleophiles: morpholine (toward **2a**−**2c**), pyrrolidine (toward **2d**−**2f**), piperidine (toward **2g**−**2i**), and *N*,*N*-dimethyl (toward **2k**) amides were all used successfully. Functional group tolerance was probed with polyfunctional compounds (**2a** and **2b**), which proved to be suitable substrates for the transformation and afforded the corresponding γ-spirobutenolides in 46% and 84% yields, respectively, with complete retention of functionality and stereocomplexity. The limited solubility of **1a** and **1b** necessitated more dilute reaction conditions, and excess *m*-CPBA was required to achieve efficient transformations for these examples. Subjecting a β-ester amide (**1c**) to the reaction conditions resulted in 30% isolated yield of spirocycle **2c**. The low yield may be partially due to the reduced nucleophilicity of the amide in this compound; however, no amide-containing spirocyclic byproducts were observed in the crude product. Exclusive formation of **2c** suggests that the amide is uniquely suited for participation in this transformation over other carbonyl groups such as esters. A simple β-furylamide afforded novel spirobutenolide **2d** in low yield (26%) despite full consumption of the starting material. *In situ* hydrolysis of bis(lactone) **2d** to a diacid product (*vide infra*) likely contributed to the poor performance of this substrate. The lack of substitution on the backbone of **1d** may also contribute to its poor performance as more highly substituted substrates may benefit from the Thorpe−Ingold effect during multiple points of the mechanism.[12] Spirocycle **2d** could also be prepared in 11% yield from the acyclic *N*,*N*-diethylamide, suggesting that both cyclic and acyclic amides are capable participants in the spirocyclization.

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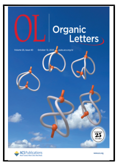

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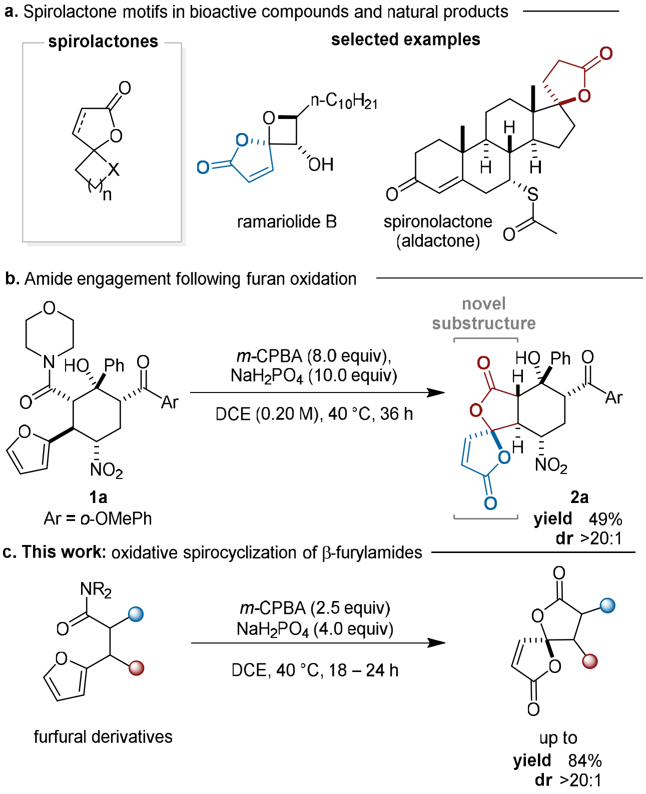
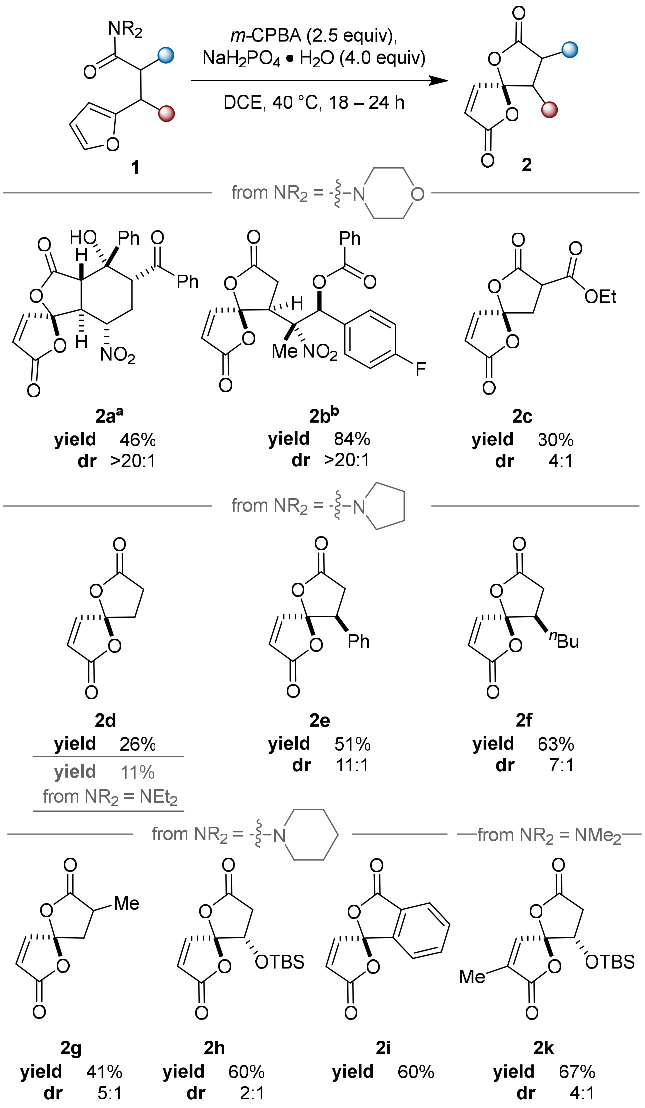
Scheme 1. (a) Spirobutenolide and Spirolactone Motifs. (b) Upon Treatment with *m*-CPBA, Exclusive Formation of a *γ*-Spirobutenolide 2a was Unexpectedly Observed. (c) Current Work Utilizing Ostensibly Poorly Reactive Amides As Tethered Nucleophiles



Aryl- and alkyl-substituted spirolactones **2e** and **2f** were isolated in reasonable yields and diastereomeric ratios (51%, 11:1 and 63%, 7:1, respectively). Methyl-substituted spirolactone **2g** was isolated as a 5:1 mixture of separable diastereomers in 41% yield. *β*-Silyloxy amide afforded **2h** in 60% yield, albeit in poor diastereoselectivity (2:1 dr). We were pleased to observe that a methyl-substituted furan could also participate in the spirocyclization reaction, delivering spirobutenolide **2k** in 67% yield as a 4:1 mixture of diastereomers. Inverse diastereoselectivity was obtained in **2h** and **2k** when compared with *β*-substituted lactones **2e** and **2f**. Unprotected furfuryl alcohols were not viable substrates for spirolactonization (*vide infra*). Using a slightly modified procedure (see Supporting Information for details), a 1.2 mmol scale reaction was performed to obtain spirobutenolide **2h** in 69% yield with 2.5:1 dr. An *ortho*-furylbenzamide was also capable of the title transformation, producing benzo-fused butenolide **2i** in 60% yield.

Having established the efficacy of the one-pot synthesis of *γ*-spirobutenolides, we were interested in probing the reaction mechanism. Several examples of *β*-furyl carbonyl oxidations have been previously reported,[13−16] some of which propose spirocyclic intermediates.[17] To observe reaction intermediates, a solution of *β*-furyl amide **1d** and the phenanthrene internal standard was prepared in $CDCl_3$ (Figure 1a, $t = 0$ min). Upon addition of 2.0 equiv *m*-CPBA, a well-precedented *cis*-ene-1,4-dicarbonyl (**Int-1**)[18] was observed in 70% yield after 10 min (NMR yield vs internal standard), identifiable by the characteristic aldehyde C−H methine resonance at δ 10.2 ppm (Figure 1a). After the solution was heated at 40 °C for 1 h, hemiacetal **Int-2** was observed. Continued heating resulted in bis(lactone) formation and ultimately production of undesired acyclic diacid **SP-1**, presumably from hydrolysis and isomerization of spirocycle **2d** ($t = 30$ h).[19] The *in situ* ^{1}H NMR spectroscopy experiments provided insights into the low yield observed for **2d** during scope exploration: oxidation of **Int-2** to **2d** appears to be the lowest-yielding step of the cascade.

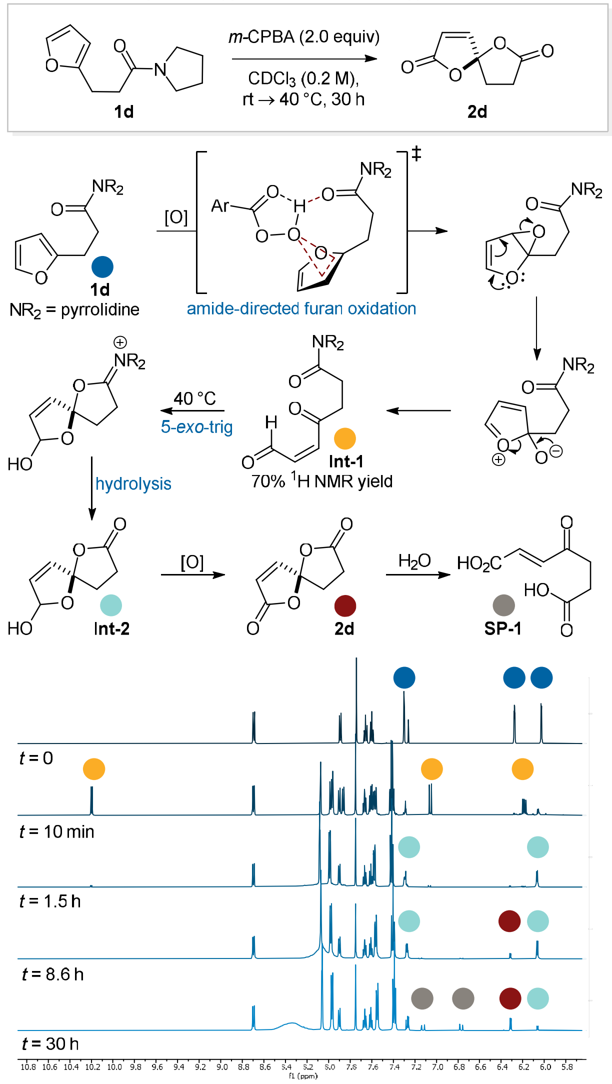
Scheme 2. Substrate Scope of Oxidative Spirocyclization[c]



[a] Reaction performed with 8.0 equiv *m*-CPBA and 10.0 equiv $NaH_2PO_4 \cdot H_2O$ on a 0.13 mmol scale. [b] Reaction performed with 8.0 equiv *m*-CPBA and 10.0 equiv $NaH_2PO_4 \cdot H_2O$ on 0.40 and 0.06 mmol scales. The reported data are the average of these two trials. [c] All reactions were performed on a 0.30 mmol scale unless otherwise noted. All yields are isolated yields. Diastereoselectivity was determined by analysis of ^{1}H NMR spectra of crude products.

Reactions of *β*-furylpropionic acid and ethyl *β*-furylpropionate with *m*-CPBA showed no evidence of spirolactone formation by ^{1}H NMR spectroscopic analysis, highlighting the unique behavior of the amide (See Supporting Information for details). Additionally, the furan oxidations from the ester and acid derivatives were much less efficient (30% and 27% ^{1}H NMR yields of *cis*-ene-1,4-dicarbonyl, respectively) when

a. *In situ* ^{1}H NMR spectroscopy informs mechanistic hypothesis



b. Competition experiment: Achmatowicz rearrangement predominates

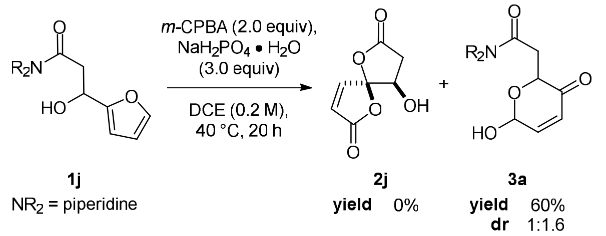


Figure 1. Mechanistic investigations of the oxidative cascade reaction. (a) Oxidation−spirolactonization−oxidation cascade observed by *in situ* ^{1}H NMR spectroscopy. (b) Proposed reaction mechanism consistent with ^{1}H NMR spectroscopy study. (c) Investigations on the reactivity of furfuryl alcohols.

compared to the amide example (70% ^{1}H NMR yield). Allylic and homoallylic amides are capable of directing *m*-CPBA alkene epoxidations;[20] these experiments collectively suggest that the amide is important in directing the initial furan oxidation by *m*-CPBA.

A plausible mechanism that accounts for the species observed *via in situ* ^{1}H NMR spectroscopy and the differences in reactivity between carbonyl identities is outlined in Figure 1a, where two separate oxidations with *m*-CPBA occur in the overall transformation. Based on the unique efficiency of furan oxidation in the presence of a tethered amide, we propose an amide-directed, dearomative epoxidation of the furan ring. The resulting bicyclic intermediate rapidly opens to reveal 1,4-dicarbonyl intermediate **Int-1**; heating the solution at 40 °C for 1 h elicits nucleophilic activity from the tethered amide in a manner similar to that observed in some lactonization protocols,[21−25] and cyclization proceeds in a 5-*exo*-trig fashion[26] to afford hemiacetal **Int-2**. Oxidation of the hemiacetal **Int-2** by *m*-CPBA affords the γ-spirobutenolide product.

This proposed mechanism suggests that an alternative oxidant might be used to convert lactol **Int-2** to spiro bis(lactone) **2d**, especially since *m*-CPBA is an unconventional reagent for lactol → lactone oxidation. A brief screen of alternative oxidants was conducted for this step, but no significant improvements in yield were obtained (see Supporting Information for details).

The α-substituted ketone **Int-1** would be the key for understanding the origin of diastereoselectivity in a kinetically controlled spirolactonization. Felkin−Anh analysis[27,28] would suggest that sterically bulkier α-keto groups would result in higher diastereoselectivity during carbonyl addition; this trend is observed (dr for **2b** > **2e** > **2f**) and is useful for the qualitative prediction of diastereoselectivity. For silyl ether substrates **2h** and **2k** where diastereoselectivity is opposite that which would be predicted by Felkin−Anh analysis, other factors may be controlling the diastereoselectivity of spirolactonization. To probe whether interconversion between diastereomers was taking place under the reaction conditions, diastereopure spirocycle **2e** was subjected to catalytic *m*-chlorobenzoic acid (*m*-CBA) in $CDCl_3$. Heating the sample at 40 °C for 20 h resulted in partial diastereomerization (**2e**:*epi*-**2e** = 21:1) and product hydrolysis (see Supporting Information for details). This experiment suggests that product thermodynamic stability contributes, at least in part, to the observed diastereoselectivity of some of the oxidative spirocyclization. This experiment also demonstrates that acidic conditions promote product hydrolysis, perhaps explaining why slightly higher yields were obtained in reactions with the added phosphonate base.

Previous reports have used organic peroxides to perform the Achmatowicz rearrangement, which converts furfuryl alcohols to dihydropyranone hemiacetals.[29,30] To probe the current method's compatibility with furfuryl alcohols as well as to understand the relative rates of the two possible reaction pathways, β-furyl amide **1j** was subjected to the standard reaction conditions (Figure 1b). Spirobutenolide **2j** was not observed, but the dihydropyranone Achmatowicz-type product **3a** was isolated as a 1:1.6 mixture of diastereomers in 60% yield. These results suggest that the 6-*exo*-trig cyclization of the Achmatowicz rearrangement is faster than the 5-*exo*-trig cyclization required to obtain the spirobutenolide product. The Achmatowicz predominance can reasonably be attributed to the higher nucleophilicity of the alcohol as compared to the amide.[31] As demonstrated with silyl ethers **2h** and **2k**, the Achmatowicz-type reactivity can be arrested by the simple protection of furfuryl alcohol groups.

Derivatizations of the γ-spirobutenolide products were investigated (Figure 2). Spirobutenolide **2e** readily participated in a Zn(II)-catalyzed Diels−Alder cycloaddition with cyclopentadiene to afford tetracycle **4a** in 67% isolated yield as an 8.5:1 mixture of separable diastereomers. The relative

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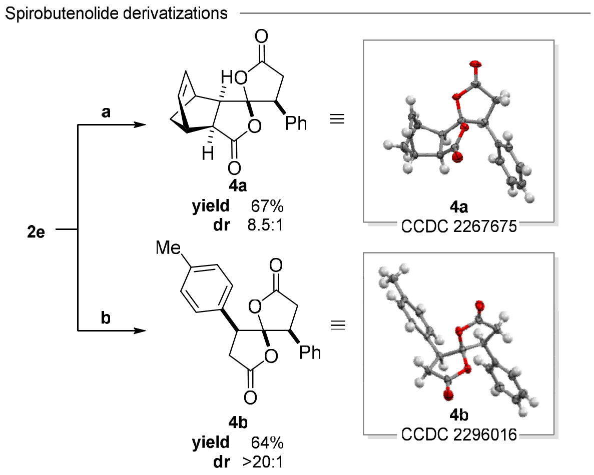

Figure 2. (a) $ZnCl_2$ (0.70 equiv), cyclopentadiene (12.0 equiv), DCM (0.65 M), rt, 18 h and (b) $[RhCl(COD)]_2$ (0.5 mol % Rh), *p*-tolueneboronic acid (3.0 equiv), CsF (5.0 equiv), Proton Sponge (1.0 equiv), 1,4-dioxane (70 mM), 50 °C, 24 h. X-ray structures of **4a** and **4b** are shown as 50% thermal ellipsoids.

configuration of the major diastereomer was established by X-ray crystallography, revealing the major stereoisomer to be the *endo* product resulting from the diene approach *syn* to the oxygen of the saturated lactone. Rhodium(I)-catalyzed arylation of spirocycle **2e** proceeded with high diastereoselectivity (>20:1 dr), and spirolactone **4b** was isolated in 64% yield. The relative stereochemistry of bis(lactone) **4b** was established by X-ray crystallography; the observed diastereomer results from addition *syn* relative to the oxygen in the butyrolactone of spirocycle **2e** (see Supporting Information for discussion of related literature examples).[11]

In conclusion, a method for the synthesis of γ-spirobutenolides from β-furyl amides using *m*-CPBA has been disclosed. The operationally simple, one-pot procedure provides access to previously unknown spirocyclic substructures. Additionally, this method represents a novel oxidative method for the cleavage of ostensibly inert amide groups under relatively mild conditions. The reported method expands the chemical space, that may be accessed from biomass-derived starting materials such as furfural and may enable broader exploration of γ-spirobutenolide architectures.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03100.

> Experimental details, materials, methods, characterization data, NMR spectra for all compounds, chromatograms for chiral separations, and information on X-ray diffraction experiments (PDF)

Accession Codes

CCDC 2267675 and 2296016 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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