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# New Synthetic Methodology Toward Azaspiro-γ-Lactones by Oxidative C–H Spirocyclization

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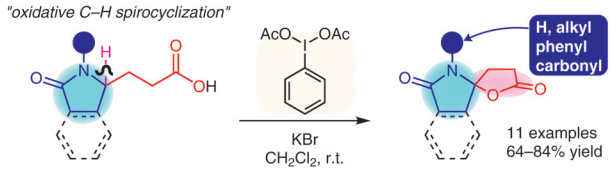


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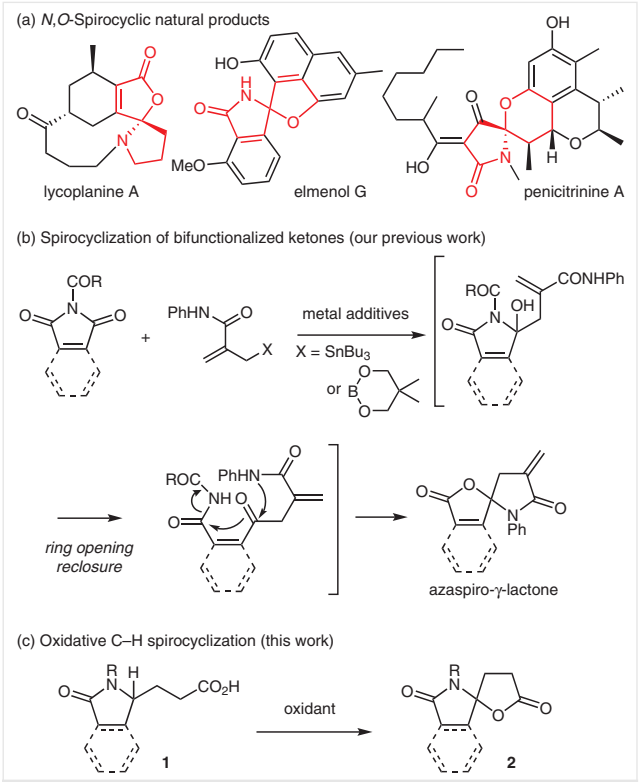
**Abstract** A new synthetic methodology for azaspiro-γ-lactones is reported. The key C–H spirolactonization was accomplished by employing iodobenzene diacetate and potassium bromide to afford a variety of azaspiro-γ-lactones in high yields. The reaction was also applicable to the preparation of a bislactone derivative.

**Key words** C–H spirolactonization, hypervalent iodine, azaspiro-γ-lactone, spiroheterocyclic compound, *N*,*O*-spirocycle

*N*,*O*-Spirocycles are often found in the core structure of natural products[1] which exhibit unique bioactivities such as calcium channel inhibitory activity (lycoplanine A),[2] tumor necrosis factor-α-related apoptosis-inducing ligand (TRAIL) resistance-overcoming activity (elmenol G),[3] and antiproliferative activity on multiple tumor types (penicitrinine A)[4] (Scheme 1, a). Several types of *N*,*O*-spirocycles have been constructed by cyclization approach using bifunctionalized ketones,[5] represented by *N*,*O*-acetalization of amino hydroxy ketones.[5f,i] Recently, we reported the analogous synthetic method starting from imide derivatives, in which a γ-hydroxylactam intermediate underwent in situ a ring opening–reclosure reaction (Scheme 1, b).[6] The product, which we call azaspiro-γ-lactone, includes an uncommon lactam spiro-fused to a lactone structure and is expected to be a precursor of thermoplastics,[7] but the substrate scope of the reaction was limited to *N*-carbonyl-substituted derivatives prepared from phthalimide and maleimide.

On the other hand, oxidative functionalization of C–H bonds has gained attention in recent years,[8] and elegant studies on the functionalization of C–H bonds adjacent to a heteroatom in heterocyclic molecules have been reported.[9] This type of transformation undoubtedly constitutes direct




**Scheme 1** Structures and synthetic methods of *N*,*O*-spirocyclic compounds

and step-economic routes toward spiroheterocyclic molecules.[10] Indeed, Corey and his co-workers demonstrated the oxidative formation of a lactone ring on the pentacyclic aspidosperma skeleton in their total synthesis of aspidophytine.[11] The White research group recently provided a synthetic example of a lactone spiro-fused to a pyrane ring through their metal (oxo)-promoted C–H hydroxylation.[12]

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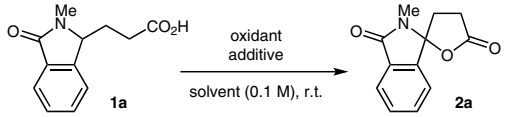
However, to our knowledge, no examples of C–H spirocyclization have been reported using a lactam derivative as a substrate to date. In this communication, we describe our development of a new synthetic method for azaspiro-γ-lactones by oxidative C–H spirolactonization at the position adjacent to a nitrogen atom of a lactam ring (Scheme 1, c).

Initially, we explored a promising oxidant for C–H spirolactonization with lactam carboxylic acid **1a**[13] bearing a relatively reactive benzylic proton. When **1a** was treated with inorganic oxidants such as cerium ammonium nitrate (CAN), iodine, potassium persulfate, and Oxone in chlorobenzene at 80 or 100 °C, only a small amount of the desired spirolactone **2a** was obtained (Table 1, entries 1–4). In contrast, iodobenzene diacectate (PIDA) that is the representative example of hypervalent iodine oxidants facilitated the spirocyclization at 100 °C to give **2a** in 71% yield along with recovery of a trace amount of starting material (entry 5). Because a subsequent attempt with an iodine(V) reagent, Dess–Martin periodinane (DMP), resulted in poor yield (entry 6), we examined the reaction using PIDA in combination with potassium bromide on the basis of the previous work relating to benzylic C–H acetoxylation reported by Kita and Dohi.[14,15] In this case, the starting material was completely consumed within 24 hours even at room temperature, giving rise to **2a** in 84% yield (entry 7).[16] Further screening of the PIDA–KBr conditions revealed that the spirocyclization is very sensitive to the reaction medium and worked well in halogenated solvents. As a result, the reaction in dichloromethane or chlorobenzene afforded **2a** in the highest yield of 84% (entries 7–12). The use of a catalytic amount of potassium bromide resulted in a reduced yield (entry 13). We then evaluated the effect of additives. When the reaction was performed with potassium fluoride, potassium chloride, or potassium iodide as an alternative to potassium bromide, the product yield was significantly decreased to 3–29% (entries 14–16). The use of the bromide salt was essential to obtain the product in good yields (entries 17–20), indicating that the C–H spirocyclization would proceed through a radical-induced hydrogen abstraction pathway.[14,17]

Thus, the optimal conditions for this transformation were determined: 1.2 equivalents of PIDA in the presence of potassium bromide (1.0 equivalents) in dichloromethane.[18,19]

Having the optimal conditions in hand, we next evaluated the scope of the spirolactonization (Scheme 2). Although the reaction of *N*-unsubstituted lactam proceeded sluggishly with poor conversions (**2b**, 13%), in the cases of *N*-alkyl, *N*-aryl, and *N*-carbonyl substrates, the corresponding azaspirolactones **2c**–**g** were obtained in high yields (77–82%). Notably, the cyclization of the *N*-benzyl derivative, which has two benzylic carbons[14] in its structure, occurred predominantly at the desired position, providing **2d** in 77% yield.[20] The poor yield of **2b** can be attributed to the low solubility of the substrate in $CH_2Cl_2$. In fact, the reaction conducted in 2,2,2-trifluoroethanol (TFE) gave **2b** in 66% yield. The attempt to construct δ-lactone fused derivative **2h** resulted in complex mixtures of undesired products as judged by the $^1$H NMR spectrum of the reaction mixture. We subsequently applied our method to the preparation of nonaromatic derivatives **2i**,**j**. This seemed to be challenging due to the fact that Kita's original protocol[14] was reported for the selective carboxylation of reactive benzylic C–H bonds. Contrary to our expectation, oxidative C–H spirolactonization successfully proceeded even at the nonactivated position by employing modified conditions (2.4 equivalents of PIDA and 2.0 equivalents of KBr at 40 °C), affording **2i** and **2j** in 87 and 64% yield, respectively. Finally, we investigated the potential for the construction of *O*,*O*-spirocycles. Reaction of lactone carboxylic acid readily proceeded under the above-mentioned modified reaction conditions, furnishing bislactone derivative **2k** in 73% yield. These results suggest

**Table 1** Screening of Conditions for Oxidative C–H Spirolactonization of **1a**




| Entry | Oxidant (equiv) | Additive (equiv) | Solvent | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1[a] | CAN (3.0) | – | PhCl | 24 | trace |
| 2[a] | $I_2$ (3.0) | – | PhCl | 6 | trace |
| 3[b] | $K_2S_2O_8$ (3.0) | – | PhCl | 12 | trace |
| 4[a] | Oxone (3.0) | – | PhCl | 6 | 7 |
| 5[a] | PIDA (3.0) | – | PhCl | 6 | 71 |
| 6[b] | DMP (3.0) | – | PhCl | 12 | 24 |
| 7 | PIDA (1.2) | KBr (1.0) | PhCl | 24 | 84 |
| 8 | PIDA (1.2) | KBr (1.0) | toluene | 24 | 13 |
| 9 | PIDA (1.2) | KBr (1.0) | MeCN | 24 | 33 |
| 10 | PIDA (1.2) | KBr (1.0) | TFE[c] | 24 | 79 |
| 11 | PIDA (1.2) | KBr (1.0) | $CHCl_3$ | 24 | 49 |
| 12 | PIDA (1.2) | KBr (1.0) | $CH_2Cl_2$ | 24 | 84 |
| 13 | PIDA (1.2) | KBr (0.2) | $CH_2Cl_2$ | 24 | 17 |
| 14 | PIDA (1.2) | KF (1.0) | $CH_2Cl_2$ | 24 | 3 |
| 15 | PIDA (1.2) | KCl (1.0) | $CH_2Cl_2$ | 24 | 14 |
| 16 | PIDA (1.2) | KI (1.0) | $CH_2Cl_2$ | 24 | 29 |
| 17 | PIDA (1.2) | NaBr (1.0) | $CH_2Cl_2$ | 24 | 46 |
| 18 | PIDA (1.2) | $ZnBr_2$ (1.0) | $CH_2Cl_2$ | 24 | 64 |
| 19 | PIDA (1.2) | CuBr (1.0) | $CH_2Cl_2$ | 24 | 65 |
| 20 | PIDA (1.2) | $Et_4NBr$ (1.0) | $CH_2Cl_2$ | 24 | 23 |

[a] Reactions were performed at 100 °C.
[b] Reactions were performed at 80 °C.
[c] TFE: 2,2,2-trifluoroethanol.

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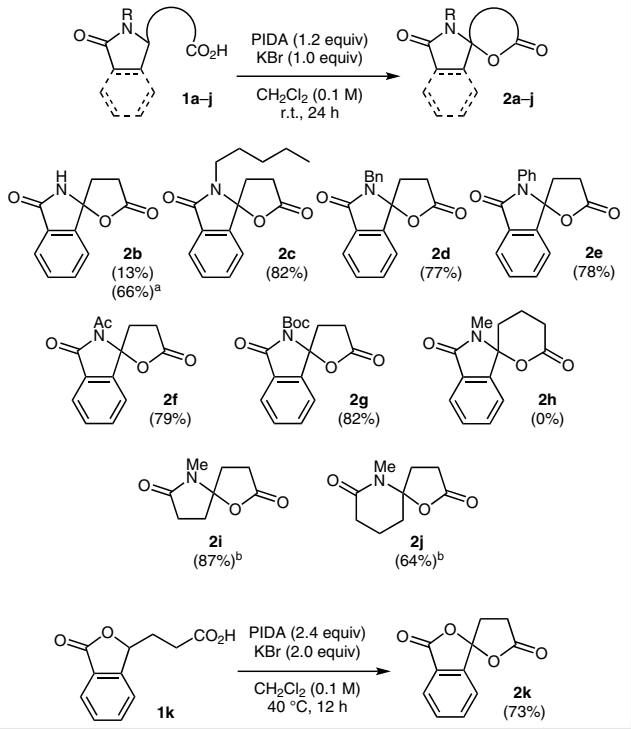
that the C–H spirocyclization reaction will have broad potential utility in the syntheses of spiroheterocyclic compounds.




**Scheme 2** Synthesis of spirolactone derivatives. [a] The reaction was performed in TFE. [b] Reactions were performed with 2.4 equiv of PIDA and 2.0 equiv of KBr for 12 h at 40 °C.

In conclusion, we have developed the new synthetic methodology for azaspiro-γ-lactones. A key outcome of this work is the PIDA/KBr-promoted C–H spirolactonization of easily accessible lactam carboxylic acids. The protocol is applicable to the preparation of the bislactone compounds as well as alicyclic azaspiro-γ-lactones. The simplicity and broad applicability of this methodology will be valuable in materials and medicinal chemistry. Further investigations into the formation of other types of spirocycles such as lactam–lactam or lactam–ether structures are underway in our laboratory, and the details of those reactions will be submitted as a full paper.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611941.

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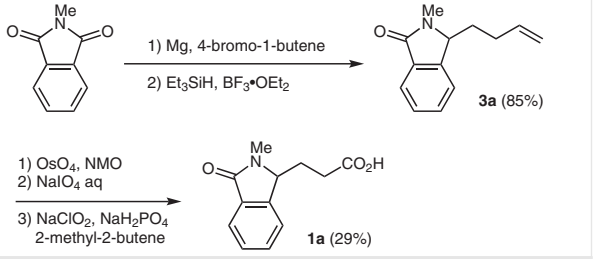
(13) Lactam carboxylic acid **1a** was readily prepared in five steps starting from commercially available *N*-methylphthalimide.




**Scheme 3**

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(15) When the reaction was performed under the classical C–H oxidation conditions (PIDA, $I_2$, h$\nu$) developed by Suárez, only 13% of product was obtained along with 43% yield of recovered starting material and a substantial amount of an unidentified side product. For Suárez's conditions, see: (a) Hernández, R.; Rivera, A.; Salazar, J. A.; Suárez, E. *J. Chem. Soc., Chem. Commun.* **1980**, 958. (b) Calvert, M. B.; Sperry, J. *Tetrahedron Lett.* **2012**, *53*, 5426.

(16) In the absence of KBr, the use of 1.2 equivalents of PIDA at room temperature gave only a trace amount of the desired product.

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(18) General procedure for spirolactonization: To a solution of **1** (21.9 mg, 0.100 mmol) in $CH_2Cl_2$ (1.0 mL) was added iodobenzene diacetate (PIDA, 38.7 mg, 0.120 mmol) and potassium bromide (11.9 mg, 0.100 mmol) at room temperature under an argon atmosphere. After stirring the suspension for 24 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was extracted with EtOAc (5 mL × 3), washed with brine (5 mL), dried with $Na_2SO_4$, filtered, and concentrated in vacuo to give a crude material. This material was purified by column chromatography on silica gel by using hexane/EtOAc as the eluent.

(19) Compound **2a**: White solid; mp 230–232 °C; IR (KBr): 1774 (C=O), 1702 (C=O) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.83 (m, 1 H, Ar*H*), 7.66–7.49 (m, 3 H, Ar*H*), 3.05 (s, 3 H, C$H_3$), 3.04–2.98 (m, 2 H, C$H_2$), 2.77 (ddd, *J* = 7.5, 9.9, 14.1 Hz, 1 H, C$H_2$), 2.60 (ddd, *J* = 7.5, 8.7, 14.1 Hz, 1 H, C$H_2$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 174.3 (*C*), 166.6 (*C*), 143.9 (*C*), 132.9 (*C*H), 130.7 (*C*H), 123.7 (*C*H), 121.4 (*C*H), 97.4 (*C*), 29.3 (*C*$H_2$), 29.2 (*C*$H_2$), 23.7 (*C*$H_3$). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.12; H, 4.88; N, 6.24.

(20) The addition of 2,2,6,6-tetramethylpiperide 1-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) to the reaction mixture of **1a** completely shut down the formation of **2a**, indicating that these reactions should be a radical process. Hydrogen abstraction from the substrate would occur at the potentially reactive C–H bond adjacent to the nitrogen atom. In the case of **2d**, hydrogen abstraction on the endocyclic carbon atom would be favored because the generated radical species could be much more stabilized by the conjugated system of isoindolinone the benzylic radical on the exocyclic position.

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