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A novel, convenient, and efficient procedure for the synthesis of spiroisoindoline-1,5′-oxazolidine derivatives

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ABSTRACT

A novel, convenient, and practical one-pot procedure for the direct synthesis of spiroisoindoline-1,5′-oxazolidine derivatives is described via oxidative cleavage of 3a,8a-dihydroxyindeno[2,1-*d*]imidazole-2,8-diones with lead(IV) acetate at room temperature.

Developing new synthetic methods for novel nitrogen-containing molecules is an important area of organic synthesis.[1] Among these compounds, isoindoline derivatives are of particular interest because of their diverse biological activities and clinical applications. The core ring structure is present in many heterocycles which have been shown to elicit a wide array of biological effects including NMDA receptor antagonism,[2a] modulation of estrogen[2b] and dopamine D3 and D4 receptors,[2c,d] inhibition of selective serotonin reuptake,[2e] and anti-bacterial activity.[2f] Similarly, oxazolidine moieties are present in many biologically active molecules of pharmaceutical interest. These ring systems have been exploited successfully in medicinally valuable compounds such as the anticancer prodrugs doxazolidine, doxoform, and doxaz carbamate.[3] These heterocyclic units are also useful intermediates for the synthesis of polymers and agricultural chemicals.[4] Several substituted oxazolidines have been investigated extensively because of their importance as chiral auxiliaries in the synthesis of a variety of chiral compounds and as chain-protecting groups for amino alcohols.[5] The vast number of transformations[1–4] reported over the last few years has led to significant interest in the chemistry of these compounds.[6]

Recently, we introduced a new procedure for the diastereoselective synthesis of highly functionalized dihydrofuran derivatives **3** by the intramolecular Wittig reaction on dihydroxyindeno[1,2-*d*]imidazole **2**, which was easily synthesized from the addition reaction of ninhydrin **1** and urea (Scheme 1).[7] In continuation of this work, and as a part of our ongoing program on ninhydrin-based reactions for the preparation of new heterocyclic derivatives,[8] we focused our attention on the oxidative cleavage of the dihydroxyindeno[1,2-*d*]imidazole derivatives **2** for the formation of the corresponding heterocycles.

Initially, we found that when a mixture of lead tetraacetate and dihydroxyindeno[1,2-*d*]imidazole[9] (**2a**) in ethanol was stirred for 3 h at room temperature, a solid compound was obtained, and its structure was characterized as 2-benzylspiro[isoindoline-1,5′-oxazolidine]-2′,3,4′-trione (**4a**) (Scheme 2) using spectroscopic data and CHN analysis.

For example, the ^{1}H NMR spectrum of **4a**[10] exhibited two distinct doublets at δ 4.54 and δ 4.75 readily recognized as arising from two diastereotopic CH_2 protons along with a singlet at δ 2.54 for the NH proton. Nine aromatic H-atoms are located as multiplets in the range of δ 7.28–7.89. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 15 distinct resonances in agreement with the proposed structure. The signals at δ 44.0, δ 153.3, δ 167.9, and δ 169.7 correlated with the benzylic CH_2 and carbonyl groups, respectively. The spiro carbon resonated at δ 95.7. The structure of product **4a** was further confirmed by mass spectrometry, which showed a molecular ion peak at 308. Finally, the structure of the product was determined unambiguously by an X-ray diffraction study (Fig. 1).

Next, the solvent and temperature were investigated to find the optimum reaction conditions. After extensive screening, we found that the reaction proceeded best in acetic acid at room temperature. Increasing the reaction temperature not only remarkably

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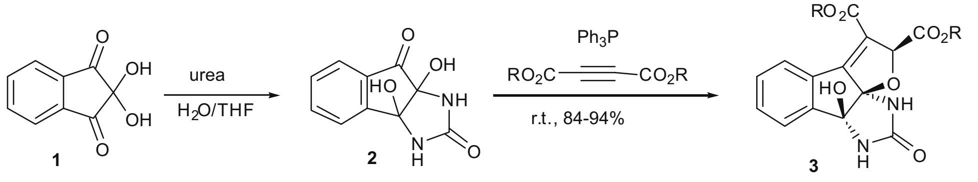
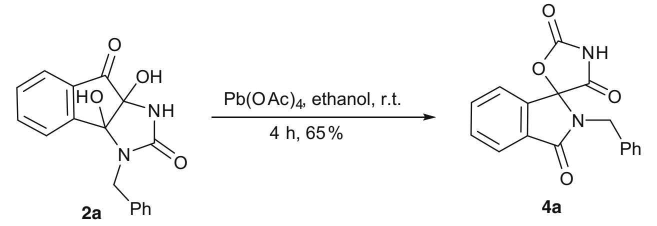


Scheme 1. Our previous work[7] on the diastereoselective synthesis of highly functionalized dihydrofurans **3**.



Scheme 2. Initial study on the oxidative cleavage of dihydroxyindeno[1,2-*d*]imidazoles **2a**.

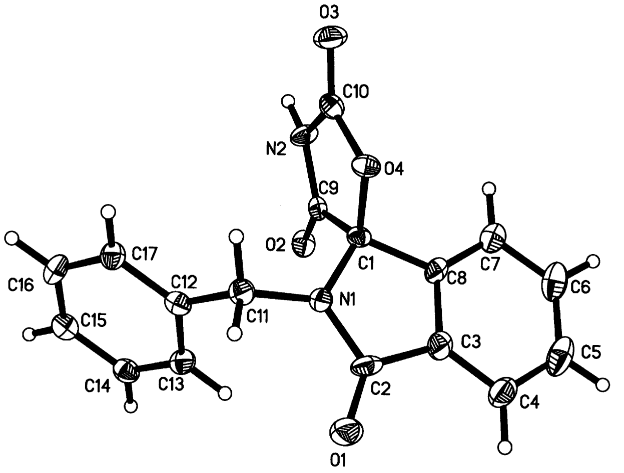
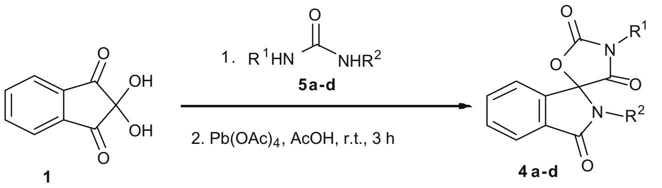


Figure 1. X-ray crystal structure of **4a**. CCDC 753345.

accelerated the reaction rate but also increased side reactions and by-product formation.

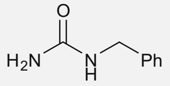
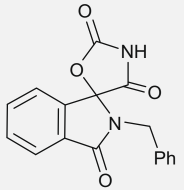
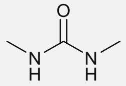
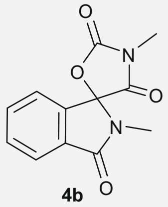
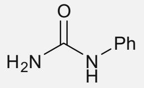
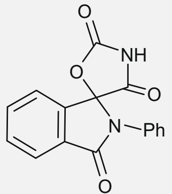
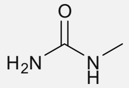
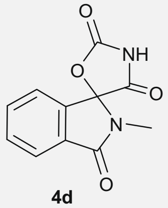
Furthermore, using this method, we obtained the spiroisoindoline-1,5′-oxazolidine derivatives **4a–d** which could also be prepared using a one-pot procedure involving the addition of lead tetraacetate to a mixture of ninhydrin **1** and urea **5** (Scheme 3). Using this one-pot procedure[10] the separation and purification steps involved with dihydroxyindeno[1,2-*d*]imidazoles **2** were eliminated and consequently, a considerable amount of time and solvent were saved. Some of the spiroisoindoline-1,5′-oxazolidine derivatives **4** were efficiently prepared using this optimized one-pot procedure and their structures were deduced from spectroscopic data and CHN analysis.[10] The results are shown in Table 1.



Scheme 3. One-pot synthesis of spiroisoindoline-1,5′-oxazolidines **4a–d**.

Table 1

One-pot synthesis of spiro[isoindoline-1,5′-oxazolidine]-2′,3,4′-trione derivatives **4**[a]

Entry	Urea	Product	Yield[b] (%)
1	 **5a**	 **4a**	84
2	 **5b**	 **4b**	75
3	 **5c**	 **4c**	73
4	 **5d**	 **4d**	80

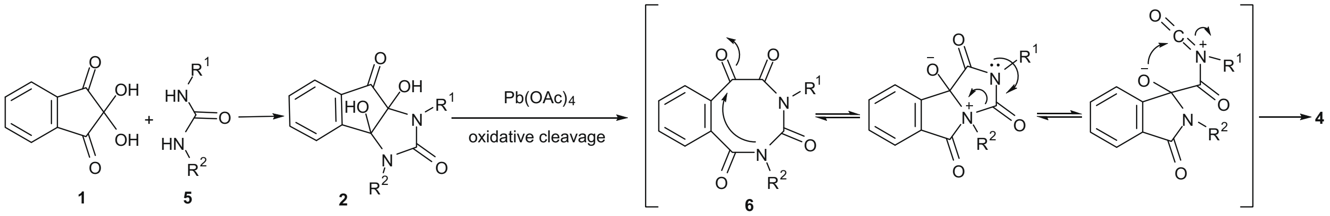
[a] All reactions were performed using 1.0 mmol of ninhydrin, 1.0 mmol of urea, and 1.5 mmol of $Pb(OAc)_4$ in 5 mL of acetic acid at room temperature.

[b] Isolated yield.

Transannular interactions and reactions among functional groups have already been identified when the donating and accepting functional groups are located at suitable positions in medium-sized (8–11-membered) ring molecules.[11] Consequently, here the formation of a benzo[*e*][1,3]diazocine-1,3,5,6(2*H*,4*H*)-tetraone intermediate **6** from the oxidative cleavage of cyclic diols **2**, involving lead tetraacetate, and its subsequent intermolecular rearrangement to the spiroisoindoline-1,5′-oxazolidines **4** is proposed as a reasonable mechanism (Scheme 4).

The reaction was very sensitive to the nature of the R^1 substituent; it progressed effectively when R^1 was a small group such as H or methyl (Table 1, entries 1–4), but no product was obtained with more bulky R^1 substituents such as phenyl, ethyl, and propyl, even on heating the reaction mixture for a longer time.

In summary, we have reported a novel transformation involving oxidative cleavage of 3a,8a-dihydroxyindeno[2,1-*d*]imidazole-2,8-diones in the presence of lead(IV) acetate, which affords spiroiso-



Scheme 4. Proposed mechanism for the formation of spiro[isoindoline-1,5′-oxazolidine]-2′,3,4′-triones **4**.

indoline-1,5′-oxazolidine derivatives. The combination of high yields, short reaction times, and mild conditions makes this method highly efficient.

Acknowledgments

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9. Dihydroxyindeno[1,2-*d*]imidazoles **2a**–**d** were obtained quantitatively from the reaction of ninhydrin **1** and urea derivatives **5** in water (or ethanol).
10. *General procedure for the one-pot preparation of spiroisoindoline-1,5′-oxazolidines* **4a**–**d**: A mixture of ninhydrin **1** (1 mmol), urea **5** (1 mmol), and ethanol (1 mL) was stirred at room temperature for 0.5 h. $Pb(OAc)_4$ (1.2 mmol) and acetic acid (2 mL) were added and the mixture was stirred for 2.5 h. Products **4a**–**d** precipitated and were easily separated from the reaction mixture by filtration. Pure product **4d** was obtained by evaporation of the solvent at room temperature and recrystallization of the crude product from *n*-hexane. *2-Benzylspiro[isoindoline-1,5′-oxazolidine]-2′,3,4′-trione* (**4a**): mp 215–217 °C; IR (KBr): $\bar{\nu}$ 3100–2924 (w), 1832 (s), 1762 (s), 1701 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.54 (s, 1H, NH), 4.54 (d, 1H, J = 15.8 Hz, CH_2), 4.75 (d, 1H, J = 15.8 Hz, CH_2), 7.28–7.32 (m, 5H, arom), 7.74–7.80 (m, 3H, arom), 7.87–7.89 (m, 1H, arom); ^{13}C NMR (125 MHz, $CDCl_3$): δ 44.0, 95.7, 122.3, 124.6, 128.4, 128.7, 128.9, 131.3, 132.0, 133.7, 135.5, 139.2, 153.3, 167.9, 169.7; Anal. Calcd for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.32; H, 3.84; N, 8.95. *m*/*z* 308 (M^+, 23%), 219 (38), 208 (34), 160 (73), 106 (100), 91 (96). *2,3′-Dimethylspiro[isoindoline-1,5′-oxazolidine]-2′,3,4′-trione* (**4b**): mp 190–191 °C; IR (KBr): $\bar{\nu}$ 1838 (s), 1760 (s), 1695 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.67 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 7.33–7.36 (m, 1H, arom), 7.55–7.76 (m, 2H, arom), 7.94–8.02 (m, 1H, arom); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.4, 26.0, 92.8, 122.8, 126.9, 128.1, 132.6, 135.8, 141.1, 155.9, 166.9, 167.4; Anal. Calcd for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.61; H, 4.00; N, 11.29. *m*/*z* 246 (M^+, 8%), 202 (100), 161 (27), 104 (45). *2-Phenylspiro[isoindoline-1,5′-oxazolidine]-2′,3,4′-trione* (**4c**): mp >300 °C; IR (KBr): $\bar{\nu}$ 3050–2930 (w), 1835 (s), 1760 (s), 1695 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.48 (m, 5H, arom), 7.52 (d, 1H, J = 6.6 Hz, arom), 7.70–7.75 (m, 2 H, arom), 7.99 (d, 1H, J = 6.5 Hz, arom), 8.68 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 96.7, 125.0, 125.6, 128.6, 129.5, 130.0, 131.1, 132.1, 132.7, 133.8, 137.7, 151.3, 167.0, 167.6; Anal. Calcd for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.37 H, 3.49; N, 9.46. *m*/*z* 294 (M^+, 100%), 224 (92), 179 (77), 76 (37). *2-Methylspiro[isoindoline-1,5′-oxazolidine]-2′,3,4′-trione* (**4d**): mp >300 °C; IR (KBr): $\bar{\nu}$ 3090–2935 (w), 1845 (s), 1766 (s), 1702 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.89 (s, 3H, CH_3), 7.67–7.94 (m, 4H, arom); ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.2, 95.7, 124.0, 124.3, 131.4, 132.8, 134.4, 139.1, 154.5, 167.4, 170.9; Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.06. Found: C, 57.05; H, 3.40; N, 12.01. *m*/*z* 232 (M^+, 63%), 162 (100), 117 (95), 104 (48), 76 (55).
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