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Tetrahedron Letters 45 (2004) 5117–5120
Tetrahedron Letters

Synthesis of 3-substituted 8-hydroxy-3,4-dihydroisocoumarins via successive lateral and *ortho*-lithiations of 4,4-dimethyl-2-(*o*-tolyl)oxazoline

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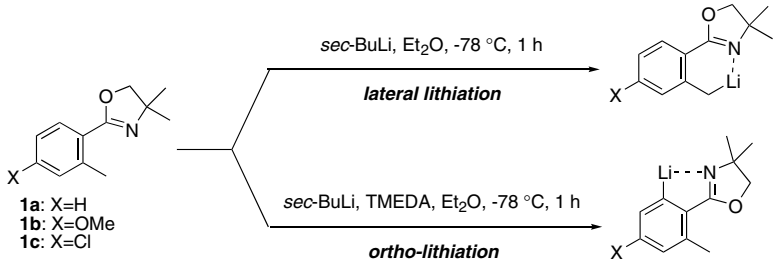
Received 1 April 2004; revised 26 April 2004; accepted 28 April 2004

Abstract—Sequential treatment of 4,4-dimethyl-2-(*o*-tolyl)oxazoline in THF with *sec*-BuLi, aromatic or aliphatic aldehydes, *sec*-BuLi, $B(OMe)_3$, and H_2O_2 produced the laterally alkylated and *ortho*-hydroxylated oxazolines in one-pot. Treatment of these products with TFA in aqueous THF provided 3-substituted 8-hydroxy-3,4-dihydroisocoumarins in 44–75% overall yields. This procedure allowed the short synthesis of (±)-hydrangenol and (±)-phyllodulcin, naturally occurring 3,4-dihydroisocoumarins of pharmacological interest. A more economical synthesis of (±)-phyllodulcin via the trianion intermediate is also described.

Directed lithiation is the most powerful method for regioselective functionalization of aromatic rings.[1] The reagent-controlled optional site-selective lithiation is especially interesting in this field from mechanistic and practical points of view.[2] Recently, we have reported that 4,4-dimethyl-2-(*o*-tolyl)oxazolines (**1a**–**c**) can be lithiated at the lateral or *ortho*-position selectively depending on the reaction conditions (Scheme 1).[3] Thus, the oxazolines were deprotonated at the most acidic lateral methyl group with *sec*-BuLi in Et_2O at −78 °C, whereas they were lithiated at the less acidic *ortho*-position with *sec*-BuLi in the presence of TMEDA. The latter unusual *ortho*-lithiation was rationalized by the unfavorable steric interaction between TMEDA and the methyl groups on the oxazoline ring in the transition state for the lateral lithiation.[3]

The 3,4-dihydroisocoumarins constitute a class of natural products, which exhibit a wide range of pharmacological activities such as antifungal,[4a] antiulcer,[4b] antileukemic,[4c] antiallergic,[4d] differentiation-inducing,[4e] and antimalarial[4f] activities. Structurally, most of these natural products possess an aryl or alkyl substituent at C-3 and a hydroxy group at C-8 of the isocoumarin core. The syntheses of this type of 3,4-dihydroisocoumarins have been achieved efficiently by



Scheme 1. Optional lateral and *ortho*-lithiations of 4,4-dimethyl-2-(*o*-tolyl)oxazolines.

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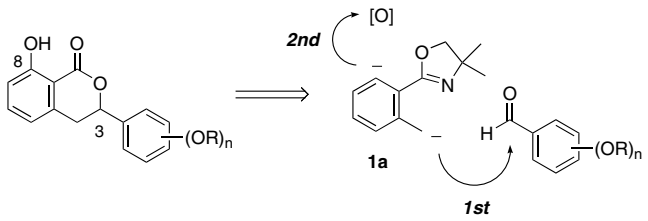
doi:10.1016/j.tetlet.2004.04.158

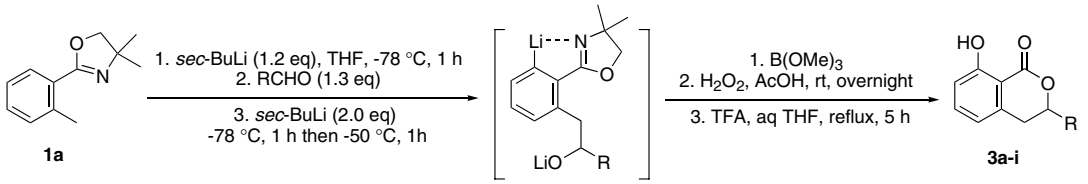


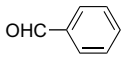
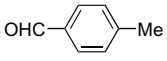
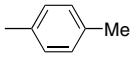
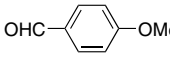
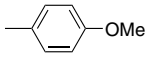
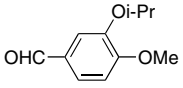
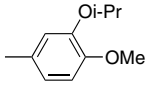
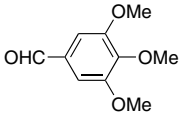
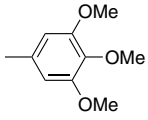
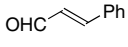
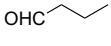
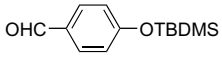
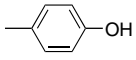
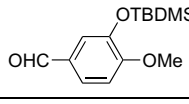
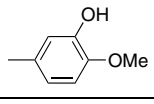
Scheme 2. Synthetic design of 3-aryl-8-hydroxy-3,4-dihydroisocoumarins.

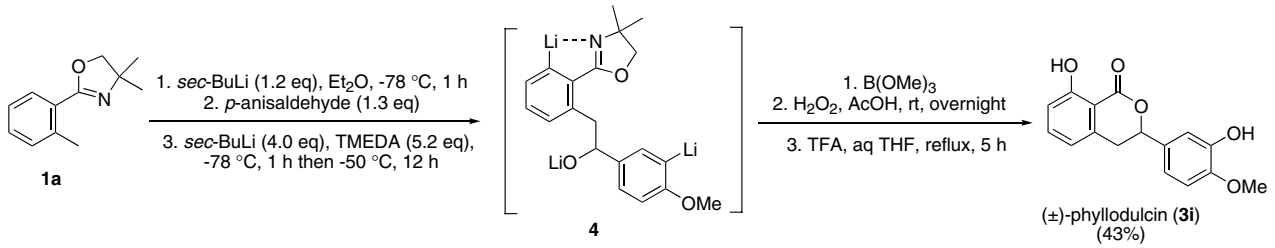
using lateral lithiation of 2-alkoxy-6-methylbenzoic acid derivatives.[5] For example, Watanabe and Snieckus have synthesized the 3,4-dihydroisocoumarin natural products, (±)-hydrangenol and (±)-phyllodulcin, via lateral lithiation of *N*,*N*-dimethyl-2-methoxy-6-methylbenzamide.[5b] We envisioned the construction of the 3,4-dihydroisocoumarins having this substitution pattern could be accomplished in one-pot via the initial lateral lithiation of 4,4-dimethyl-2-(*o*-tolyl)oxazoline (**1a**) followed by addition to an aldehyde, the second *ortho*-lithiation, and oxidation (Scheme 2). In this article, we report a highly efficient synthesis of the 3-substituted 8-hydroxy-3,4-dihydroisocoumarins based upon this strategy.

The synthesis of the desired dihydroisocoumarins has been achieved most satisfactorily as follows.[6] The oxazoline **1a** was lithiated at the lateral position with *sec*-BuLi (1.2 equiv) in THF at −78 °C and the generated deep red anion was trapped with an appropriate aldehyde. Subsequently, the addition product was treated with *sec*-BuLi (2.0 equiv) at −78 °C for 1 h and then at −50 °C for 1 h to effect *ortho*-lithiation. The presumed intermediate **2** thus generated was hydroxylated by sequential treatment with $B(OMe)_3$ and H_2O_2. After extractive workup, the crude product was treated with TFA in refluxing aqueous THF to give 3-substituted 8-hydroxy-3,4-dihydroisocoumarin **3**. Yields of **3a**–**i** thus synthesized are summarized in the Table 1. A variety of aromatic aldehydes including cinnamaldehyde were subjected to reaction in good yields to give the corresponding 3,4-dihydroisocoumarins (entries 1–6). Although the yield was modest, an enolizable aliphatic aldehyde was successfully employed in this synthesis (entry 7). In the reactions with *O*-TBS-protected *p*-hydroxybenzaldehyde and isovanillin, (±)-hydrangenol (**3h**) and (±)-phyllodulcin (**3i**), respectively, were obtained directly in fair yields (entries 8 and 9). The silyl protecting group may be removed during the final TFA treatment. These natural products are the principal

Table 1. Synthesis of 3-substituted 8-hydroxy-3,4-dihydroisocoumarins **3a**–**i**



Entry	Aldehyde	Dihydroisocoumarin	R	**3** (%)
1		**3a**		71
2		**3b**		75
3		**3c**		67
4		**3d**		56
5		**3e**		57
6		**3f**		60
7		**3g**	*n*-Pr	44
8		**3h**		59
9		**3i**		53



Scheme 3. Synthesis of (±)-phyllodulcin (**3i**) via the trianion intermediate **4**.

constituents of Amacha (Hydrangeae Dulcis Folium), a natural medicine indigenous to Japan, produced from the leaves of *Hydrangea macrophylla* Seringe var. *thunbergii* Makino.[7] The sweet taste of Amacha is caused by (+)-phyllodulcin, which has been reported to be 400 times as sweet as sucrose.[8]

Related to this lithiation-based synthesis of dihydroisocoumarins, we devised a more economical synthesis of (±)-phyllodulcin, in which the use of protected isovanillin is avoided (Scheme 3).[9] The oxazoline **1a** in Et_2O was sequentially treated with *sec*-BuLi (1.2 equiv) at −78 °C for 1 h, *p*-anisaldehyde, *sec*-BuLi (4.0 equiv) in the presence of TMEDA at −78 °C for 1 h and at −50 °C for 12 h to generate the trianion intermediate **4**. Subsequently, **4** was quenched with $B(OMe)_3$ and then oxidized with H_2O_2 in the presence of AcOH. The crude product was treated with TFA in refluxing aqueous THF for 5 h to give (±)-phyllodulcin (**3i**) in 43% yield. It is noteworthy that the use of Et_2O as a solvent and TMEDA as an additive is critical for the efficient generation of **4**.

In summary, we have developed a new general synthesis of 3-substituted 8-hydroxy-3,4-dihydroisocoumarins, including (±)-hydrangenol and (±)-phyllodulcin, via successive lateral and *ortho*-lithiations of 4,4-dimethyl-2-(*o*-tolyl)oxazoline (**1a**). A specific but exceptionally efficient synthesis of (±)-phyllodulcin is also devised. In view of the easy availability of **1a** from commercially available inexpensive *o*-toluic acid,[10] we believe the methods developed herein are most convenient and economical for the synthesis of this class of compounds.

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6. *Typical procedure* (*synthesis of* **3a**). Under an argon atmosphere, oxazoline **1a** (207 mg, 1.09 mmol) was dissolved in dry THF (5 mL) and the solution was cooled to −78 °C. A solution of *sec*-BuLi in cyclohexane–hexane (0.960 M, 1.36 mL, 1.31 mmol) was added dropwise to this solution. After stirring for 1 h, a solution of benzaldehyde (144 μL, 1.42 mmol) in dry THF (4 mL) was added, and the mixture was stirred for 1 h at −78 °C. To this solution, *sec*-BuLi in cyclohexane–hexane (0.960 M, 2.27 mL, 2.18 mmol) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C and for 1 h at −50 °C. After cooling to −78 °C, $B(OMe)_3$ (367 μL, 3.28 mmol) was added as a neat liquid. The mixture was stirred for 1 h at −78 °C, allowed to warm to room temperature, and stirred for 2 h. After addition of AcOH (375 μL, 6.55 mmol) and 30% H_2O_2 (670 μL, 6.55 mmol), the mixture was stirred for 16 h at room temperature. Water was added and the mixture was extracted with Et_2O. The extract was washed successively with 10% aqueous $NaHSO_3$ and brine, dried over Na_2SO_4, and evaporated to leave an oily product. A mixed solution of this product in THF (10 mL)–water (1.5 mL)–TFA (0.5 mL) was refluxed for 5 h under argon atmosphere. After cooling, the mixture was basified with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated. The residue was

purified by flash chromatography over silica gel (CH_2Cl_2–hexane = 1:1) to give 8-hydroxy-3-phenyl-3,4-dihydroisocoumarin (**3a**) (188 mg, 71%).

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9. *Procedure*. Under an argon atmosphere, oxazoline **1a** (210 mg, 1.11 mmol) was dissolved in dry Et_2O (5 mL) and the solution was cooled to −78 °C. A solution of *sec*-BuLi in cyclohexane–hexane (0.870 M, 1.53 mL, 1.33 mmol) was added dropwise to this solution. After stirring for 1 h, a solution of *p*-anisaldehyde (175 μL, 1.44 mmol) in dry Et_2O (4 mL) was added dropwise and the mixture was stirred for 1 h at −78 °C. TMEDA (869 μL, 5.76 mmol) was added and the mixture was stirred for 10 min. A solution of *sec*-BuLi in cyclohexane–hexane (0.870 M, 5.09 mL, 4.43 mmol) was added dropwise, and the mixture was stirred for 1 h at −78 °C and for 12 h at −50 °C. After cooling to −78 °C, $B(OMe)_3$ (745 μL, 6.65 mmol) was added as a neat liquid. The reaction mixture was stirred for 1 h at −78 °C, allowed to warm to room temperature, and stirred for 2 h. After addition of AcOH (760 μL, 13.3 mmol) and 30% H_2O_2 (1.36 mL, 13.3 mmol), the reaction mixture was stirred for 22.5 h at room temperature. Water was added and the mixture was extracted with Et_2O. The extract was washed successively with 10% aqueous $NaHSO_3$ and brine, dried over Na_2SO_4, and evaporated to leave an oily product. A mixed solution of this product in THF (10 mL)–water (1.5 mL)–TFA (0.5 mL) was refluxed for 5 h under argon atmosphere. After cooling, the mixture was basified with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel (CH_2Cl_2–hexane = 5:1 to CH_2Cl_2–ethyl acetate = 20:1) to give (±)-phyllodulcin (**3i**) (137 mg, 43%).
10. Generally, 3-substituted 8-hydroxy-3,4-dihydroisocoumarins are prepared from a common starting material, ethyl 2-hydroxy-6-methylbenzoate. The synthesis of this compound, however, requires a couple of tedious steps and harmful reagents, see: Hauser, F. M.; Pogany, S. A. *Synthesis* **1980**, 814–815; For a recent synthesis of dihydroisocoumarin natural products from this starting material, see: Günes, M.; Speicher, A. *Tetrahedron* **2003**, *59*, 8799–8802.