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Radical-mediated synthesis of 3,4-dihydroisocoumarins: total synthesis of hydrangenol

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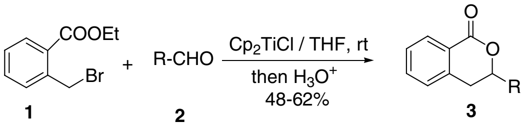
Abstract—A radically promoted synthesis of 3,4-dihydroisocoumarins has been achieved in moderate to good yields using titanocene(III) chloride (Cp_2TiCl) as the radical initiator. The total synthesis of (±)-hydrangenol has been completed using this radical technology. Cp_2TiCl was prepared in situ from commercially available titanocene dichloride (Cp_2TiCl_2) and Zn-dust in THF under argon.

3,4-Dihydroisocoumarins constitute a class of naturally occurring lactones, which exhibit a wide range of biological activities[1] such as antifungal, antiallergenic, antileukemic, antiulcer and antimalarial activities as well as sweetness properties. They are also used as key intermediates in the synthesis of various bioactive natural products.[2] Most of these natural products possess an aryl or alkyl substituent at C-3 of the lactone moiety and a hydroxyl group at C-8 of the aromatic ring of the core structure. A number of methods have been reported for the synthesis of 3,4-dihydroisocoumarins mainly following lateral- and *ortho*-lithiations[3] along with other strategies.[4] However, many of these methods suffer from harsh reaction conditions, multi-step procedures and inefficiencies due to functional group intolerance. The mildness and efficiency of radical-mediated reactions have significantly encouraged synthetic chemists in recent years to utilize radical technology in developing novel methods and applications in natural product synthesis. In continuation of our studies on the synthesis of natural products through radical-induced reactions,[5] we report a radical-mediated method to construct C-3 substituted 3,4-dihydroisocoumarins **3** in a single operation with moderate to good yields from ethyl 2-bromomethyl benzoate (**1**) and aldehydes **2** using dicyclopentadienyl titanocene(III) chloride (Cp_2TiCl) as the radical initiator (Scheme 1).



Scheme 1.

The radical initiator, Cp_2TiCl, can easily be prepared from commercially available titanocene dichloride (Cp_2TiCl_2) and zinc dust in THF.[6]

Thus, a series of 3,4-dihydrocoumarins **3a**–**j** has been prepared from various aryl and alkyl aldehydes **2a**–**j** via radically promoted synthesis[7] and the results are summarized in Table 1. The substrates underwent radical induced Barbier-type reaction[8] followed by lactonization to furnish product **3**. Reaction of **1** with allyl and propargyl substituted salicylaldehydes **2h** and **2i** (Table 1, entries 8–9) furnished the expected dihydroisocoumarins **3h** and **3i**, respectively, without any intramolecular cyclization as reported previously by us.[5i] This is probably due to the fact that formation of radicals from benzyl bromides with Cp_2TiCl is much faster than with aldehydes. Ketones, such as cyclohexanone and acetophenone, yielded only self-coupling products in the presence of Cp_2TiCl.

After successful experiments with different aldehydes, we applied this radical technology to the synthesis of naturally occurring (±)-hydrangenol (**7**), a dihydroisocoumarin, isolated from *Hydrangea opuloides Steud.*

Keywords: Titanocene(III) chloride; Radical reaction; 3,4-Dihydroisocoumarins; Hydrangenol.

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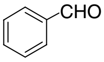
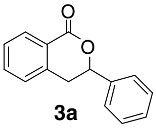
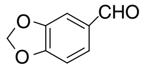
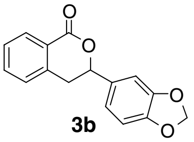
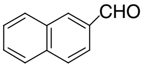
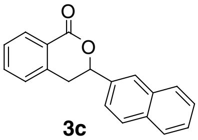
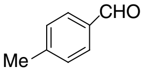
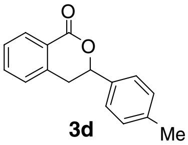
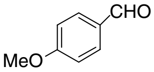
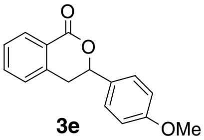
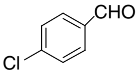
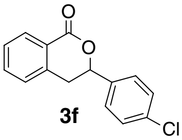
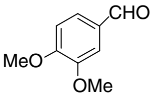
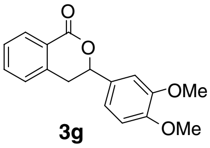
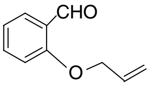
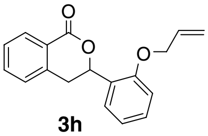
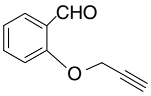
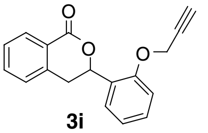
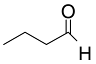
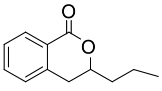
Table 1. Radically promoted synthesis of 3,4-dihydroisocoumarins

Entry	Aldehyde	Product[a]	Yield[b] (%)
1	 **2a**	 **3a**	62
2	 **2b**	 **3b**	59
3	 **2c**	 **3c**	51
4	 **2d**	 **3d**	60
5	 **2e**	 **3e**	56
6	 **2f**	 **3f**	48
7	 **2g**	 **3g**	53
8	 **2h**	 **3h**	54
9	 **2i**	 **3i**	56
10	 **2j**	 **3j**	53

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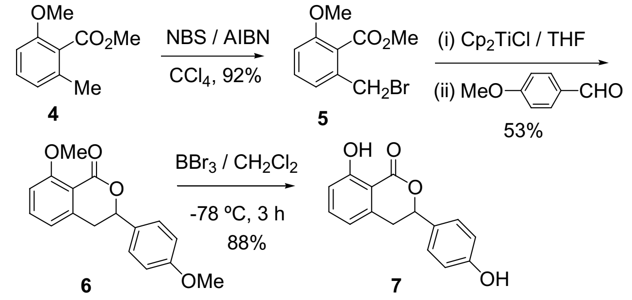
[a] All products were obtained following a similar procedure to that described in Ref. 7 and were characterized by IR, NMR, and HRMS.

[b] Yields refer to pure isolated products.

var. otakusa.[9] Readily available[10] methyl 2-methyl-6-methoxybenzoate (**4**) was used as the starting material. Compound **4** on bromination with NBS in the presence of a catalytic amount of AIBN yielded bromide **5** in 92% yield. Bromide **5**, on treatment with Cp_2TiCl in THF under argon at room temperature in the presence of 4-methoxybenzaldehyde (**2e**), followed by quenching afforded lactone **6** in 53% yield as a crystalline solid,



Scheme 2.

mp 152–154 °C (Scheme 2). Demethylation of **6** with boron tribromide in CH_2Cl_2 afforded (±)-hydrangenol (**7**)[11] in 88% yield[12] as colorless crystals, mp 179–181 °C (lit.[10] mp 181 °C).

In conclusion, we have developed a mild radical-induced method for the synthesis of C-3 substituted 3,4-dihydroisocoumarins using titanium(III) chloride as the radical initiator. This methodology has also been applied successfully to the total synthesis of (±)-hydrangenol.

Acknowledgments

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7. *Typical procedure:* A red solution of Cp_2TiCl_2 (747 mg, 3.0 mmol) in deoxygenated THF (40 mL) was stirred with activated zinc dust (130 mg, 2 mmol) (activated zinc dust was prepared by washing 20 g of commercially available zinc dust with 60 mL of 4 N HCl followed by thorough washing with water until the washings became neutral and finally washing with dry acetone and then drying in vacuo) under argon until it turned green. This green solution was transferred to a dropping funnel via cannula and was added dropwise over 9 h to a solution of bromide **1** (364 mg, 1.5 mmol) and aldehyde **2b** (225 mg, 1.5 mmol) in THF (20 mL). The reaction mixture was then stirred for an additional 4 h. After completion of the reaction (monitored by TLC), it was quenched slowly with 25% aqueous H_2SO_4. Most of THF was removed under reduced pressure and resulting residue was extracted with diethyl ether (3 × 25 mL). The organic layer was washed successively with water (2 × 10 mL), brine (2 × 10 mL), and finally dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude material obtained was purified by column chromatography over silica gel (ethyl acetate in light petroleum) to furnish **3b** (237 mg, 59%) as a crystalline solid, mp 138–140 °C; IR (KBr): 1705, 1448, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.05 (dd, $J = 3.0$, 16.4 Hz, 1H), 3.28 (dd, $J = 12.0$, 16.4 Hz, 1H), 5.42 (dd, $J = 3.0$, 12.0 Hz, 1H), 5.95 (s, 2H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.89 (dd, $J = 1.0$, 8.0 Hz, 1H), 6.95 (d, $J = 1.0$ Hz, 1H), 7.25 (d, $J = 7.3$ Hz, 1H), 7.39 (dd, $J = 7.5$ Hz, 1H), 7.54 (dd, $J = 7.5$ Hz, 1H), 8.10 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.5, 78.8, 100.2, 105.7, 107.2, 118.9, 124.0, 126.3, 126.8, 129.3, 131.3, 132.8, 137.8, 146.8, 146.9, 164.2; HRMS Calcd for $C_{16}H_{13}O_4$ $[M^+ + H]$ 269.0808. Found: 269.0849.
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12. *Synthesis of (±)-hydrangenol* (**7**): A solution of boron tribromide (1 M, 2 mL) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of dimethyl ether **6** (142 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The reaction mixture was then allowed to warm to room temperature and was stirred for an additional 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and then extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was washed successively with water (2 × 10 mL), brine (2 × 10 mL), and finally dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude material obtained was purified by column chromatography over silica gel (30% ethyl acetate in light petroleum) to furnish **7** (113 mg, 88%) as colorless crystals, mp 179–181 °C (lit.[10] mp 181 °C); IR (KBr): 3354, 1658, 1460, 1230, 1028 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.10 (dd, $J = 2.5$, 16.4 Hz, 1H), 3.37 (dd, $J = 12.0$, 16.4 Hz, 1H), 5.63 (dd, $J = 2.5$, 12.0 Hz, 1H), 6.80 (d, $J = 8.2$ Hz, 2H), 6.83–6.89 (m, 2H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.50 (dd, $J = 7.9$ Hz, 1H), 9.62 (s, 1H, phenolic OH), 10.92 (s, 1H, phenolic OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.4, 81.4, 109.3, 116.1, 116.3, 119.2, 129.2, 129.3, 137.2, 141.5, 158.7, 161.8, 170.2; HRMS Calcd for $C_{15}H_{12}O_4Na$ $[M^{+}+Na]$ 279.0633. Found: 279.0649.