Novel $AlCl_3$ Catalysed Syntheses of Naturally Occurring (±) 8-Hydroxy-3-methyl-3,4-dihydroisocoumarins

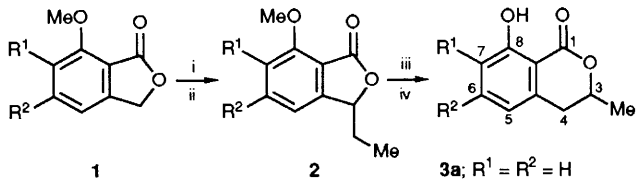
Raghao S. Mali,* Prakash G. Jagtap, Shrikant R. Patil and Prakash N. Pawar

Garware Research Centre, Department of Chemistry, University of Poona, Ganeshkhind, Pune 411 007, India

Treatment of (±) 3-ethylphthalides **2** or 2-(prop-1-enyl)benzoic acids **5** with $AlCl_3$ in methylene chloride gives naturally occurring (±) 8-hydroxy-3-methyl-3,4-dihydroisocoumarins **3** in high yields.

A large number of 8-hydroxy-3-methyl-3,4-dihydroisocoumarins **3** have been isolated from natural sources.[1] The parent compound mellein **3a** is widespread in nature and isolated from various microorganisms.[1] 8-Hydroxy-3-alkyl-3,4-dihydroisocoumarins are known to possess antifungal, insecticidal and antitumor activities.[1] 8-Hydroxy-3,4-dihydroisocoumarins such as AI-77s[1] have been found to exhibit unique antiulcerogenic activity against stress ulcers in rats without anticholinergic, antihistamineric and central suppressive effects.[2] In view of this several methods have been developed for their synthesis.[1–4] In this communication we report two different approaches for the synthesis of (±) 8-hydroxy-3-methyl-3,4-dihydroisocoumarins **3**. A recent report[4] which makes use of 2-(prop-1-enyl)benzoic acids for the synthesis of (±)8-hydroxy-3-substituted-3,4-dihydroisocoumarins **3** prompted us to publish our results.

In our first approach (Scheme 1) the phthalide anions obtained by reaction of phthalides[5] **1a–d** with LDA in THF at −78 °C for 10 min, were treated with ethyliodide (−78 to 0 °C for 1–2 h) to give the corresponding (±) 3-ethylphthalides **2a–d**. Treatment of phthalides **2a, c, d** with anhydrous $AlCl_3$ in methylene chloride at room temperature for 1–2 h (monitored by TLC) provided (±) 8-hydroxy-3-methyl-3,4-dihydroisocoumarins **3a, c, d** in 78, 72 and 68% yield, respectively. In the case of (±) 5,6,7-trimethoxy-3-ethylphthalide **2b** along with (±) kigelin (**3b**, 61%) a minor amount of (±) 7-demethylkigelin (**3e**, 10%) was also obtained. The position of hydroxy groups in **3e** was confirmed by NOE experiment.



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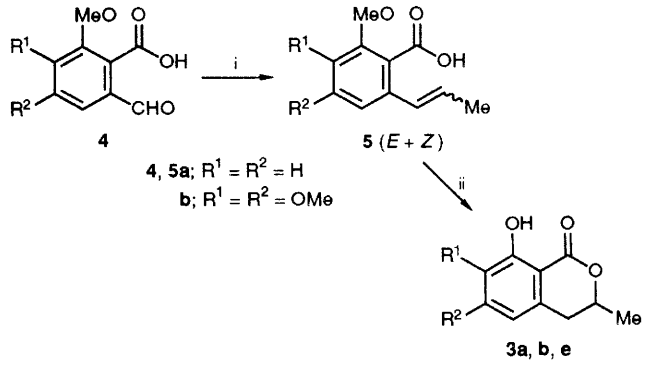
1, 2a; $R^1 = R^2 = H$
b; $R^1 = R^2 = OMe$
c; $R^1 = H$, $R^2 = OMe$
d; $R^1 = OMe$, $R^2 = H$

3a; $R^1 = R^2 = H$
b; $R^1 = R^2 = OMe$
c; $R^1 = H$, $R^2 = OMe$
d; $R^1 = OME$, $R^2 = H$
e; $R^1 = OH$, $R^2 = OMe$

Scheme 1 *Reagents and conditions*: i, LDA, THF, −78 °C; ii, EtI; iii, $AlCl_3$, CH_2Cl_2



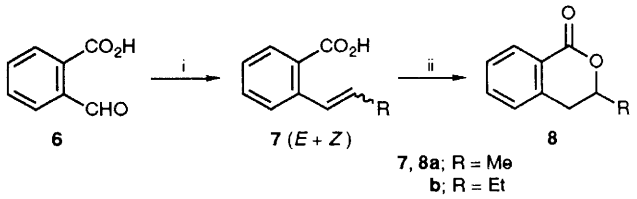
Scheme 2 *Reagents and conditions*: i, $Ph_3P^+EtBr^-$, $KOBu^t$; ii, $AlCl_3$, CH_2Cl_2

In the second approach (Scheme 2), a mixture of (*E*)- and (*Z*)-2-(prop-1-enyl)benzoic acids **5a–b** synthesised from phthalaldehydric acids[6] **4a–b** using Wittig reaction, were treated with $AlCl_3$ in methylene chloride at room temperature to provide the corresponding (±) 8-hydroxy-3-methyl-3,4-dihydroisocoumarins **3a, b** in 86 and 66% yield, respectively. In the case of **5b** along with **3b** (66%), a minor amount of **3e** (10%) was also isolated. In these methods $AlCl_3$ acts as a reagent for the conversion of phthalides **2** and 2-(prop-1-enyl)benzoic acids **5** into the corresponding (±) 8-methoxy-3-methyl-3,4-dihydroisocoumarins and for selective demethylation[7] of C_8-methoxy group.

To demonstrate the generality of this reaction, (±) 3-alkyl-3,4-dihydroisocoumarins **8a–b** have also been synthesised in high yields (85 and 81%, respectively) from a mixture of (*E*)- and (*Z*)-2-vinylbenzoic acids[8] **7a–b** using $AlCl_3$ (Scheme 3).

The IR and ^1H NMR spectral data of isocoumarins **3a–c**, **3e** and **8a** are identical with those reported[7,9,10]. Isocoumarin **3d** also exhibited satisfactory analytical and spectral data.†

The present approaches demonstrate the synthetic utility of $AlCl_3$ and also provide exclusively isocoumarins **3** and **8** from the corresponding (±) 3-ethylphthalides **2** and 2-(alk-1-enyl)-benzoic acids (**5** and **7**). These routes appear to be more attractive than the recently reported method,[4] which gives a mixture of isocoumarins and phthalides under variety of conditions from 2-(prop-1-enyl)benzoic acids.



Scheme 3 *Reagents and conditions*: i, Ph_3P^+ CH_2–RBr^-, $KOBu^t$; ii, $AlCl_3$, CH_2Cl_2

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† **3d**: ^1H NMR ($CDCl_3$, 90 MHz) δ 1.50 (d, *J* 6.5 Hz, 3H, CH_3), 2.86 (d, *J* 8 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.52–4.88 (m, 1H, C_3H), 6.61 (d, *J* 9 Hz, 1H, ArH), 6.97 (d, *J* 9 Hz, 1H, ArH), 11.2 (s, exchangeable with D_2O, 1H, OH).