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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 7539–7543

Efficient and general method for the synthesis of benzopyrans by ethylenediamine diacetate-catalyzed reactions of resorcinols with α,β-unsaturated aldehydes. One step synthesis of biologically active (±)-confluentin and (±)-daurichromenic acid

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Received 9 June 2005; revised 30 August 2005; accepted 31 August 2005
Available online 15 September 2005

Abstract—An efficient and general synthesis of benzopyrans is achieved by ethylenediamine diacetate-catalyzed reactions of resorcinols with α,β-unsaturated aldehydes in moderated yields. As an application of this methodology, biologically interesting confluentin, which was known to have an inhibitory effect on histamine release is synthesized in one step. Also, natural daurichromenic acid, which has highly potent anti-HIV activity, is successfully synthesized in one step.

The compounds containing benzopyran moiety (chromenes) are widely distributed in nature.[1] They have shown many biological activities[2] and are used as versatile intermediates in organic and natural product synthesis.[3] Several synthesis of benzopyran nuclei have been reported using the Claisen rearrangement of propargyl ethers[4] and Lewis acid-catalyzed condensation of phenols with acetals or ketals.[5] These reactions have been limited due to harsh reaction conditions, long reaction steps, unsatisfactory yields, and stoichiometric amounts of catalysts. As a useful strategy for the synthesis of benzopyrans, cycloaddition of phenols to α,β-unsaturated aldehydes have been reported in refluxing pyridine.[6] These reactions have limitations such as low yields and difficulty of isolation of the products. In order to overcome limitations of this process, metal-catalyzed reactions have been developed by several groups.[7]

Ethylenediamine diacetate-catalyzed reactions of 1,3-dicarbonyl compounds with enals have received considerable attention due to their highly catalytic activity.[8] These reactions provided a rapid entry to versatile heterocycles by tandem Knoevenagel-electrocyclic reaction. In order to increase reactivity and yields of tandem Knoevenagel-electrocyclic reactions of 1,3-dicarbonyl compounds, cycloaddition using α,β-unsaturated iminium salts has been also reported by Hsung and co-workers.[9] However, ethylenediamine diacetate-catalyzed reactions of substituted resorcinols instead of 1,3-dicarbonyl compounds to α,β-unsaturated aldehydes have not been reported. We report herein an efficient and convenient procedure for the synthesis of benzopyrans starting from resorcinol in the presence of ethylenediamine diacetate.

Reaction of orcinol (**1**) with 3-methyl-2-butenal was investigated under several catalysts (Table 1). Both indium(III) chloride (10 mol %) and ytterbium(III) triflate (10 mol %) as Lewis acid catalysts in refluxing acetonitrile gave no adducts. With pyridine as a reactant and solvent, no products were obtained. Treatment of **1** 3-methyl-2-butenal in the presence of 20 mol % of $Ca(OH)_2$ according to Shigemasa condition[10] gave no products. Interestingly, with ethylenediamine diacetate (10 mol %) as a catalyst, products **2** and **3** were obtained. Upon raising the temperature to 80–140 °C by using the several solvents, the best yields of **2** (55%) and **3** (5%) were obtained in toluene. The two compounds were easily separated by column chromatography and assigned by spectroscopic analyses.[11]

Additional reactions of several types of resorcinols with α,β-unsaturated aldehydes were carried out in the presence of ethylenediamine diacetate (10 mol %) in toluene

Keywords: Benzopyrans; Ethylenediamine diacetate.
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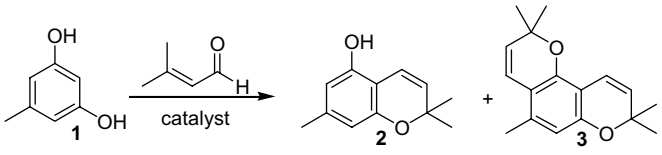
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.08.159

Table 1. Reaction of **1** with 3-methyl-2-butenal under several catalysts



Catalyst (mol %)	Condition	Yield (%)	
		2	**3**
$InCl_3$ (10)	Acetonitrile, reflux, 5 h	0	0
$Yb(OTf)_3$ (10)	Acetonitrile, reflux, 5 h	0	0
Pyridine (excess)	Reflux, 5 h	0	0
$Ca(OH)_2$ (20)	Rt, 12 h	0	0
Ethylenediamine diacetate (10)	CH_2Cl_2, rt, 12 h	11	0
Ethylenediamine diacetate (10)	Benzene, reflux, 5 h	36	6
Ethylenediamine diacetate (10)	Toluene, reflex, 5 h	55	5
Ethylenediamine diacetate (10)	Xylene, reflux, 5 h	33	8

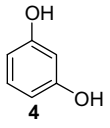
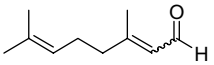
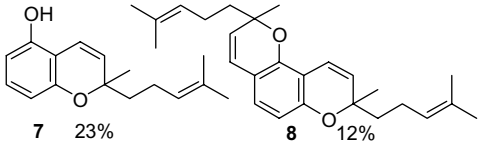
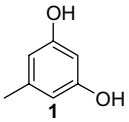
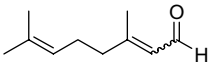
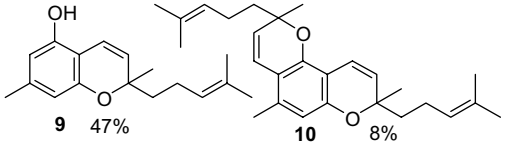
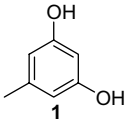
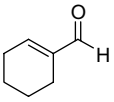
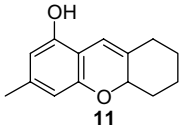
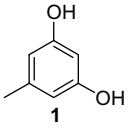
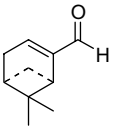
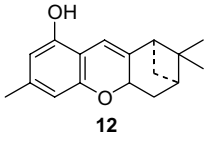
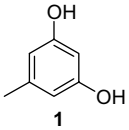
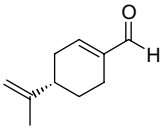
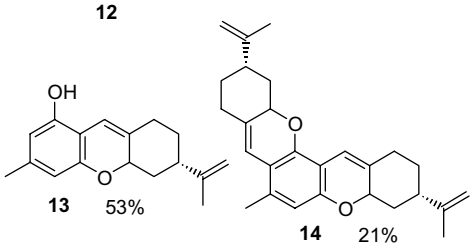
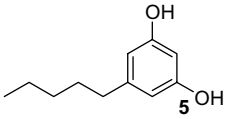
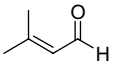
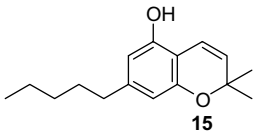
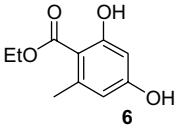
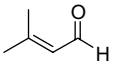
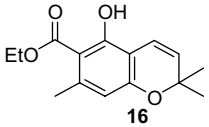
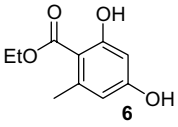
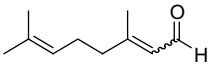
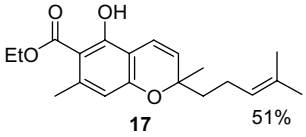
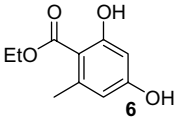
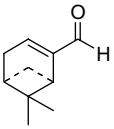
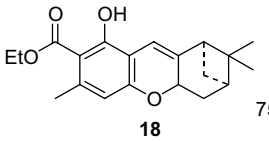
or xylene. The results are collected in Table 2. Reaction of resorcinol (**1**) with 3-methyl-2-butenal in refluxing xylene for 5 h afforded adducts **7** and **8** in 23% and 12% yields, respectively (Table 2, entry 1). In the case of resorcinols with substituent on the ring, a higher yield of products was produced. For example, reaction of orcinol (**1**) with citral under 10 mol % of ethylenediamine diacetate in refluxing toluene for 5 h gave both **9** and **10** in 47% and 8% yields, respectively (entry 2). With other α,β-unsaturated aldehydes including cyclic ring, cycloaddition reactions were successful. Reactions of **1** with 1-cyclohexene-1-carboxaldehyde and (−)-myrtenal provided adducts **11** (62%) and **12** (78%) as a single compound, respectively (entries 3 and 4), whereas treatment with (−)-perillaldehyde in refluxing xylene gave both **13** and **14** in 53% and 21% yields (entry 5). On the other hand, in reaction with a long chain on the resorcinol ring, reaction was also successful. Reaction of **5** with 3-methyl-2-butenal in refluxing toluene afforded adduct **15** in 48% yield (entry 6). In order to extend the utility of this methodology, further reactions with other types of substituted resorcinol were examined (entries 7–9). Reaction of ethyl 2,4-dihydroxy-6-methylbenzoate (**6**) with 3-methyl-2-butenal in refluxing xylene afforded **16** in 60% yield. Similarly, with citral and (−)-myrtenal in refluxing toluene or xylene, adducts **17** and **18** were obtained in 51% and 75% yields, respectively. These reactions provide a rapid route for the synthesis of benzopyran derivatives with a variety of substituents on the benzopyran ring.

As an application of this methodology, total synthesis of confluentin (**19**) and daurichromenic acid (**20**) was next attempted. Confluentin (**19**) was recently isolated from *Rhododendron dauricum*, a plant found in areas of northern China, eastern Siberia, Mongolia, and Hokkaido, Japan (Fig. 1).[12] The dried leaves of this plant are known as 'Manshanfong' in China and are used in medicines for treatment of an expectorant and an acute-chronic bronchitis.[13] Confluentin (**19**) has shown an inhibitory effect on histamine release.[12] Daurichromenic acid (**20**), rhododaurichromanic acid A (**21**), and rhododaurichromanic acid B (**22**) were also isolated from the same plant.[14] Daurichromenic acid (**20**) has shown highly potent anti-HIV activity in acutely infected H9 cells with an EC_{50} of 0.00567 μg/mL and a therapeutic index (TI) of 3710. Rhododaurichromanic acid A (**21**) has also shown potent anti-HIV activity with an EC_{50} value of 0.37 μg/mL and a TI of 91.9.[14] Interestingly, although natural confluentin and daurichromenic acid have been isolated from same sources, their absolute configurations of C-2 are different. The absolute configuration of **19** is known as *R* from its circular dichroism spectrum by Kitanaka and co-workers.[12] The absolute stereochemistry of **20** was confirmed as *S* from X-ray crystallographic analysis and photochemical conversion by Kashiwada et al.[14]

The one-step synthesis of confluentin (**19**) is outlined in Scheme 1. Reaction of orcinol (**1**) with *trans*,*trans*-farnesal in the presence of 10 mol % of ethylenediamine diacetate at refluxing xylene for 5 h gave adduct **19** in 65% yield. The spectroscopic data of our synthetic material **19** are in agreement with those reported in the literature.[15]

Recently, the total synthesis of daurichromenic acid (**20**), rhododaurichromanic acid A (**21**), and rhododaurichromanic acid B (**22**) has been reported by three groups. Hsung and co-workers have reported on total synthesis of methyl ester of **20** starting from 5-methyl-1,3-cyclohexanedione in three steps (22%, overall yields).[16] Subsequent photochemical reaction and hydrolysis of methyl ester of **20** gave rhododaurichromanic acid A (**21**) and rhododaurichromanic acid B (**22**) as a mixture. Other synthetic approach of daurichromenic acid (**20**) was accomplished by Jin and co-workers starting from orcinol in five steps (49%, overall yields).[17] Compound **20** provided **21** (40%) and **22** (20%) by irradiation with a low-pressure mercury lamp. More recently, another concise synthesis of **20** has been reported by Wilson and co-workers from ethyl acetoacetate in four steps (6%, overall yields).[18] Although there are currently several methods available to synthesize daurichromenic acid (**20**), rhododaurichromanic acid A (**21**), and rhododaurichromanic acid B (**22**), general and efficient concise synthetic routes are still more required. Our one-step synthetic approach to dauri-

Table 2. Reaction of resorcinols with α,β-unsaturated aldehydes

Entry	Starting material	α,β-Unsaturated aldehyde	Condition	Product (yield)
1	 **4**		B	 **7** 23% **8** 12%
2	 **1**		A	 **9** 47% **10** 8%
3	 **1**		B	 **11** 62%
4	 **1**		B	 **12** 78%
5	 **1**		B	 **13** 53% **14** 21%
6	 **5**		A	 **15** 48%
7	 **6**		B	 **16** 60%
8	 **6**		B	 **17** 51%
9	 **6**		A	 **18** 75%

Condition A: ethylenediamine diacetate (10 mol %), toluene, reflux, 5 h.
Condition B: ethylenediamine diacetate (10 mol %), xylene, reflux, 5 h.

chromenic acid (**20**) is shown in Scheme 2. Reaction of **6** with *trans*,*trans*-farnesal in the presence of 10 mol % of ethylenediamine diacetate at refluxing benzene for 5 h gave adduct **20** in 59% yield. The spectroscopic data of our synthetic material **20** are in agreement with those reported in the literature.[14]

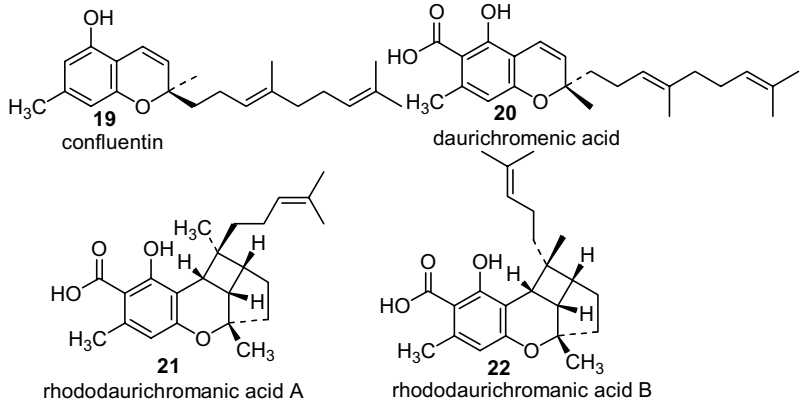
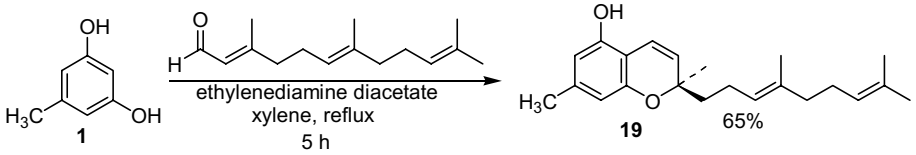
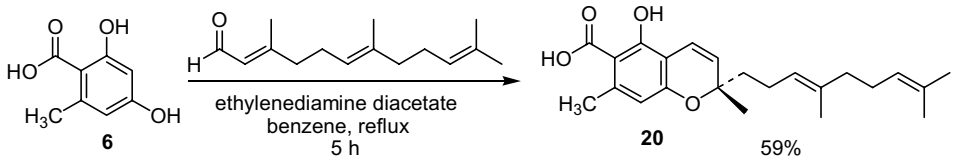


Figure 1.



Scheme 1.



Scheme 2.

In conclusion, we have described here the formation of benzopyrans starting from resorcinols with α,β-unsaturated aldehydes in the presence of ethylenediamine diacetate. This methodology has been applied to the total synthesis of naturally occurring confluentin (**19**) and daurichromenic acid (**20**).

Acknowledgment

This work was supported by a research grant from the Advanced Research Center at Yeungnam University (105096).

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