Et_2AlCl PROMOTED COUPLING REACTIONS OF 4-HYDROXY-2-PYRONE OR 4-HYDROXYCOUMARINE WITH ALDEHYDES: SYNTHESIS OF METHYLENEBIS(4-HYDROXY-2-PYRONE) OR METHYLENEBIS(4-HYDROXYCOUMARINE) DERIVATIVES[1]

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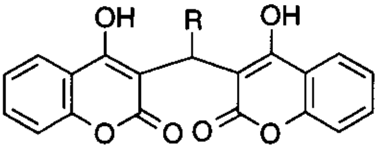
Abstract-Methylenebis(4-hydroxy-2-pyrone) or methylenebis(4-hydroxy-coumarine) derivatives (**5**) have been synthesized from 4-hydroxy-2-pyrones (**6**) and (**8**) or 4-hydroxycoumarine (**10**) with aldehydes (**4**) in the presence of diethylaluminum chloride.

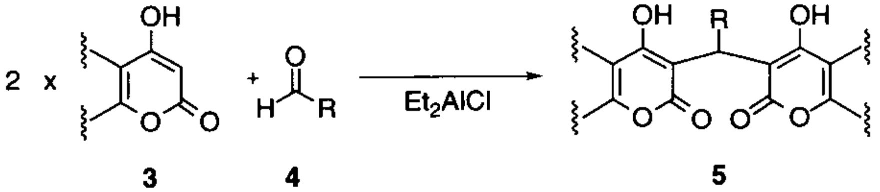
The polyketide derivatives originating from 4-hydroxypyrone and 4-hydroxycoumarine are widely distributed in nature.[2] These compounds are well known for their characteristic biological activity and especially, the methylene bridged biscoumarins (**1**) (dicoumarol) and (**2**) (coumetarol) find application as oral anticoagulants and have been introduced in medicine to treat prophylaxis of thromboemblic disorders.[3,4] Although some precedents do exist in literature to obtain methylene-bis(4-hydroxy-2-pyrone) derivatives (**5**) by condensation of 4-hydroxycoumarine (**10**) with aqueous formaldehyde under basic condition to afford **1**,[4] through electrochemical oxidation of **3**,[5] and under Knoevenagel reaction conditions from **8**,[6] the first method lacks generality as it involves aqueous reaction media and the second procedure is useful to obtain only the methylene bridged bispyrone derivatives (**5**) (R=H).



1 R=H Dicoumarol
2 $R=CH_2OMe$ Coumetarol

In connection with the synthetic studies directed towards some natural products, we were on lookout for a general and improved procedure to link two units of 4-hydroxy-2-pyrone derivatives (**3**) with aldehydes (**4**) in an attempt to obtain methylenebis(4-hydroxy-2-pyrone) derivatives (**5**) in substantial yield (Scheme 1).

Scheme 1. Coupling of 4-hydroxy-2(2*H*)-pyrone derivatives with aldehydes



When the reaction of coumarin (**10**) with hexanal under aqueous condition in presence of base was carried out by following the literature procedure,[4] the coupling product (**11c**) was obtained in only 20% yield. The poor yield so obtained, prompted us to work-out alternate procedures for the preparation of **11c** and accordingly, we investigated the reaction of hydroxypyrone (**6**) with paraformaldehyde in presence of Lewis acid under aprotic medium leading to methylenebispyrone (**7**). Among the Lewis acids used for the reaction, it was observed that diethylaluminum chloride (Et_2AlCl) in dichloromethane at room temperature under nitrogen atmosphere gave better yields of coupling product (Table 1) compared to other Lewis acids. Whereas ethylethoxyaluminum chloride and titanium dichlorobisisopropoxide proved to be ineffective resulting in recovery of the substrate, reaction in aqueous medium using ytterbium triflate[7] furnished the coupling product (**7**) in 31% yield (Entry 1). Not only formaldehyde alone but also other aldehydes were reacted under the reaction conditions employed. The polarity of the solvent used also found to influence to certain extent the product yield. In some cases (Entries 6 and 8) depending on the nature of the substrate used, more polar solvents such as 1,2-dichloroethane or acetonitrile gave improved yields than less polar solvent like toluene. In the reaction with 3-phenylpropionaldehyde, elevated temperature provided better yields (Entry 6). In case of benzaldehyde and acetone, the starting 4-hydroxy-2-pyrone (**6**) was recovered unchanged probably as a result of steric and electronic factors.

A plausible reaction pathway for the formation of coupling products (**5**) promoted by Et_2AlCl can be rationalized as shown in Scheme 2.

Scheme 2. Reaction pathway

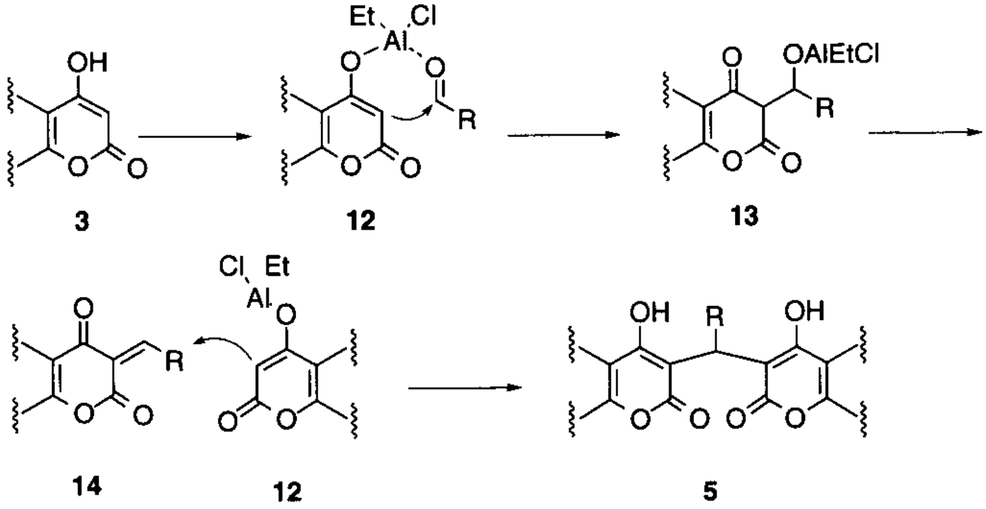
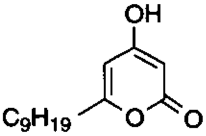
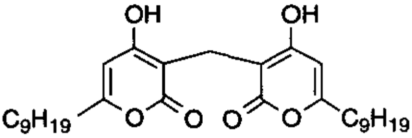
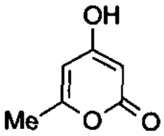
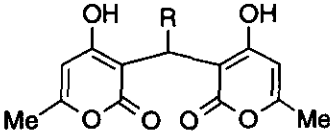
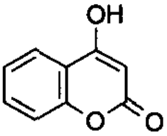
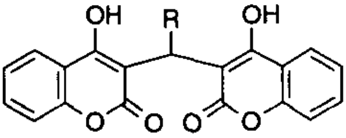


Table 1. The reactions of 4-hydroxypyrones and 4-hydroxycoumarine with aldehydes

Entry	Starting Material		Reagent and Conditions[a]	Products and Yields (%)	
	Pyrone	R-CHO			
	 **6**			 **7**	
1		$(CH_2O)_n$	$Yb(OTf)_3$/THF-H_2O, 12 h		31
2			Et_2AlCl/toluene, 12 h		72
3			Et_2AlCl/CH_2Cl_2, 1 h		82
	 **8**				
4		R=H (gas)	Et_2AlCl,[b] 24 h	**9a**:R=H	65
5		R=CH_2CH_2Ph	Et_2AlCl,[b] 70 h	**b**:R=CH_2CH_2Ph	30
6			Et_2AlCl,[c,d] 30 h		85
7			$EtAlCl_2$,[c] 23 h		50
8		R=C_5H_{11}	Et_2AlCl,[e] 22 h	**c**:R=C_5H_{11}	80
9			$EtAlCl_2$,[c] 40 h		54
10		R=C_9H_{19}	Et_2AlCl,[e] 40 h	**d**:R=C_9H_{19}	41
	 **10**				
11		R=H (gas)	Et_2AlCl,[b] 4.5 h	**11a**:R=H	60
12		R=CH_2CH_2Ph	Et_2AlCl,[e] 23 h	**b**:R=CH_2CH_2Ph	41
13		R=C_5H_{11}	Et_2AlCl,[e] 37 h	**c**:R=C_5H_{11}	64
14		R=C_9H_{19}	Et_2AlCl,[e] 20 h	**d**:R=C_9H_{19}	81

[a] The reaction was carried out at rt unless otherwise indicated.
[b] Dichloromethane was used.
[c] 1,2-Dichloroethane was used.
[e] Acetonitrile was used.
[d] The reaction was carried out at 55 °C.

Generation of aluminum enolate (**12**) is suggested as there was generation of gas probably of ethane when diethylaluminum chloride was added to the hydroxypyrone (**3**). Subsequent aldol condensation with aldehyde (**4**) followed by β-elimination provided a non-isolable highly reactive 2-methylenepyrone intermediate (**14**). Addition of second molecule of **12** to **14** in 1,4-fashion furnished methylenebis(4-hydroxy-2-pyrone) derivative (**5**).

In conclusion, we have clearly established that substituted methylenebis(4-hydroxy-2-pyrone) or methylenebis(4-hydroxycoumarine) derivatives (**5**) can be conveniently prepared from their respective parent compounds through diethylaluminum chloride assisted condensation with corresponding aldehydes in satisfactory yields.

Typical experimental procedure:To a stirred solution of 4-hydroxycoumarine (**10**) (81 mg, 0.5 mmol) in acetonitrile (5 mL) was added diethylaluminum chloride (1.1 mL, 1 mmol, 0.96 M solution in *n*-hexane) and subsequently decanal (61μL, 0.5 mmol) under nitrogen atmosphere. After being stirred for 3 h, decanal (61μL, 0.5 mmol) was added and stirring was continued for 17 h at rt. The reaction was quenched by addition of ice. After filtration through celite pad, aqueous layer was extracted with dichloromethane twice. Evaporation of the solvent followed by flash column chromatography ($MeOH:CHCl_3=1:50$) afforded **11d** (94 mg, 81%) which had IR ($CHCl_3$) ν_{max} 2986, 1730, 1657, 1620, 1468, 1375, and 1269 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.83 (t, 3H, *J* 7.5 Hz), 1.10~1.45 (br s, 10H), 1.45~1.70 (br s, 2H), 2.25~2.55 (br t, 2H, *J* 8 Hz), 4.47 (t, 1H, *J* 8.9 Hz), 7.30~7.40 (m, 2H), 7.53~7.64 (m, 2H), and 7.97~8.04 (m, 2H).

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