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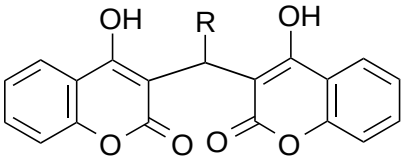
SYNTHESIS OF METHYLENEBIS(4-HYDROXY-2-PYRONE) OR METHYLENEBIS(4-HYDROXYCOUMARIN) DERIVATIVES BY ORGANIC SOLID STATE REACTION[1]

Hisahiro Hagiwara,*[a] Norikazu Fujimoto,[b] Toshio Suzuki,[a] and Masayoshi Ando[b]

Graduate School of Science and Technology,[a] and Faculty of Engineering,[b] Niigata University, 8050, 2 no-cho, Ikarashi, Niigata 950-2181, Japan

Abstract–Methylenebis(4-hydroxy-2-pyrone) or methylenebis(4-hydroxy-coumarin) derivatives (**5**) have been synthesized from 4-hydroxy-2-pyrones or 4-hydroxycoumarin (**3**) with aldehydes (**4**) by organic solid state reaction.

The methylene bridged biscoumarins namely dicoumarol (**1**) and coumetarol (**2**) find application as oral anticoagulants in the treatment of thromboemblic disorders,[2,3] besides retaining their role as reagents for biochemical use. Some literature precedents do offer methods to synthesize these compounds, for example, methylenebis(4-hydroxy-2-coumarin) derivatives (**5**) was prepared by condensation of 4-hydroxycoumarin (**3**) with aqueous formaldehyde under basic condition.[3] Similarly, the electrochemical oxidation[4] and the treatment of **6** under Knoevenagel reaction conditions[5] are the other alternative procedure described for the preparation of these bis compounds. However, 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 (**11a**).

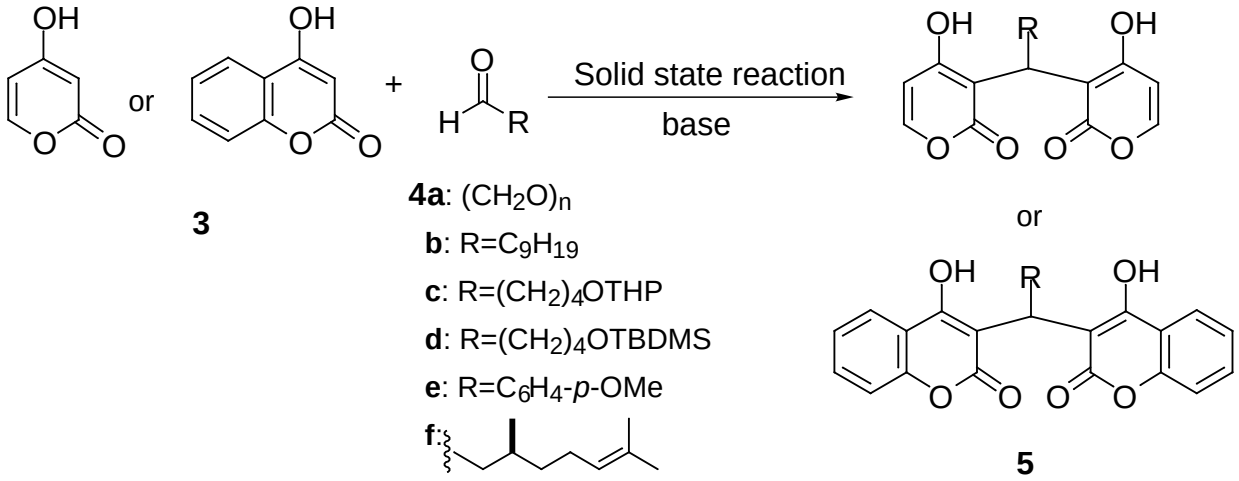


1 R=H Dicoumarol
2 R=CH_2OMe Coumetarol

In connection with the synthetic studies directed towards some natural products together with our continued interest in the organic solid state reaction,[6] we delineate herein a general and alternative procedure to combine two units of 4-hydroxy-2-pyrone derivatives (**3**) with aldehydes (**4**) to provide methylenebis(4-hydroxy-2-pyrone) derivatives (**5**) simply by grinding the substrates in a mortar (Scheme 1).

Recently, we reported Et_2AlCl promoted coupling of 4-hydroxy-2-pyrone or 4-hydroxycoumarin derivatives (**3**) leading to methylenebis(4-hydroxy-2-pyrone) or methylenebis(4-hydroxycoumarin) derivatives (**5**)[7] in good yield.

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



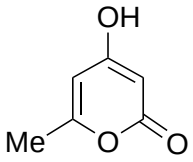
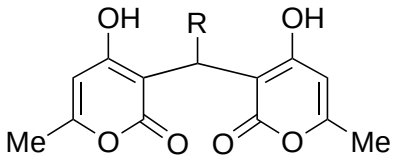
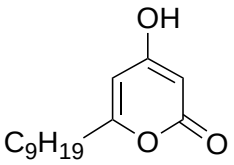
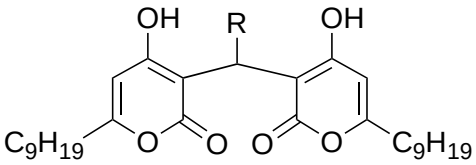
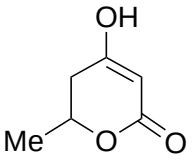
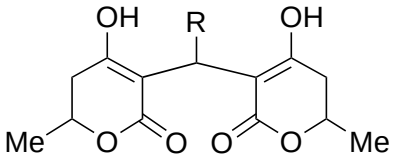
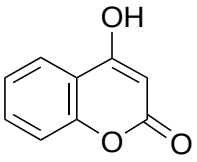
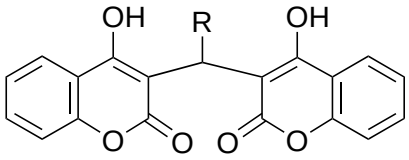
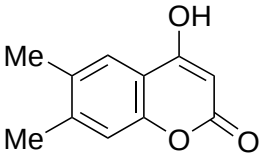
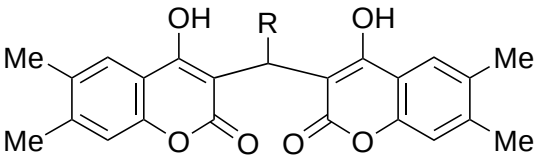
Though our previous procedure cited above offered some advance in preparing compounds (**5**), one of the difficulties in carrying out the reaction is the low solubility of starting pyrones or coumarin derivatives (**3**) in the solvents. Another drawback was the low yields of coupling products (**5**) derived from aldehydes (**4c**) and (**4d**) having acid sensitive THP or TBDMS protecting group, electron rich aldehydes such as *p*-anisaldehyde (**4e**), or acid sensitive substrates like citronellal (**4f**). In order to overcome these limitations, we turned our attention to basic solid state reaction whose utility is well recognized[8] though application to synthetic organic chemistry has been limited.

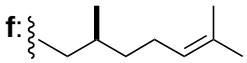
The proper reaction condition was investigated by using 6-methyl-4-hydroxypyrone (**6**) or 4-hydroxycoumarin (**9**) with paraformaldehyde. Among the bases used for the reaction, coupling reaction proceeded to give constant yields of products with DBU. Potassium carbonate gave comparable yields though the reaction was sluggish. On the other hand, organic solid base such as dimethylaminopyridine gave poor yields. Without base, the reaction resulted in complete recovery of starting materials. The reaction was carried out by simple grinding of a mixture of pyrone (**3**), aldehyde (**4**) and DBU in a mortar with a pestle in open air at ambient temperature. Products (**5**) were directly purified by silica gel column chromatography.

Some representative results are listed in Table 1. Not only 4-hydroxypyrones (**6**) and (**7**), or 4-hydroxycoumarins (**9**) and (**10**), but also 5,6-dihydro-4-hydroxy-(2*H*)-pyrane (**8**) afforded dimeric products (**11** ~ **15**) in fair to good yield. It is noteworthy that *p*-anisaldehyde (**4e**) provided coupling product in high yield.[7] In Entry 4, low purity of aldehyde (**4d**) resulted in low yield of the product. In Entry 19, substantial amount of aldehyde (**4e**) (39%) was recovered back due to interruption of the reaction at earlier stage. Self condensation of aldehydes (**4**) was not a problem under the present basic reaction conditions.

In order to demonstrate the utility of this method, the present procedure was applied to the synthesis of bisnorhelipyrone (**20**) isolated from the roots of *Helichrysum arenarium*[9] (Scheme 2). β,δ-Diketo ester (**18**) was prepared by condensation of methyl propionylacetate dianion with acetaldehyde followed by Jones oxidation. Base assisted cyclization[10] of **18** gave pyrone derivative (**19**) whose solid state reaction with paraformaldehyde in the presence of DBU furnished bisnorhelipyrone (**20**) in high yield.

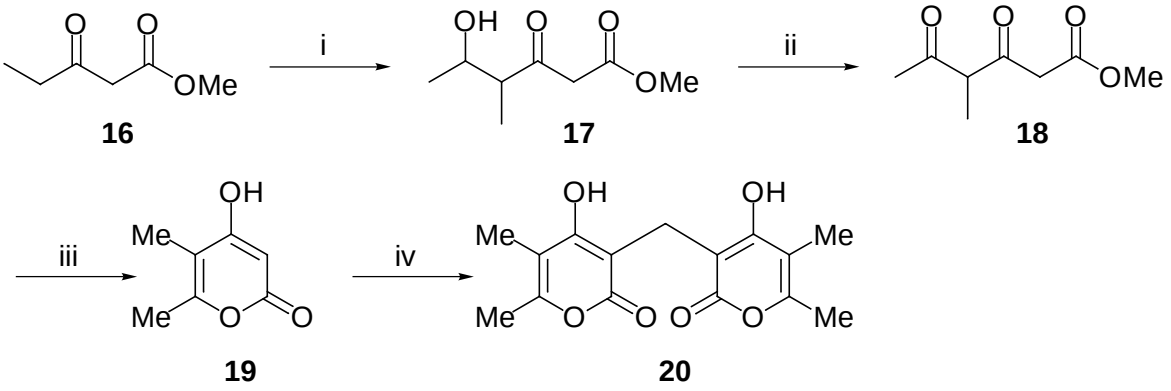
Table 1. Solid state reactions of 4-hydroxypyrones, 5,6-dihydro-4-hydroxypyrone, and 4-hydroxycoumarin with aldehydes

Entry	Starting Material Pyrone	R-CHO	DBU/ Condition (eq/ h)	Products	Yield (%)[a]
1		**4a**:	0.2/ 2		**11a**: 62
2		**b**:	0.1/ 5		**b**: 80
3		**c**:	0.1/ 24		**c**: 81
4		**d**:	0.2/ 26		**d**: 47
5	**6**	**e**:	0.2/ 9	**11**	**e**: 99
7		**4a**:	0.4/ 2		**12a**: 73
8		**e**:	0.4/ 4		**e**: 64
	7			**12**	
9		**4a**:	0.4/ 1.2		**13a**: 87
10		**b**:	0.4/ 3		**b**: 61
11		**e**:	0.4/ 1.5		**e**: 78
	8			**13**	
12		**4a**:	0.4/ 24		**14a**: 65
13		**b**:	0.1/ 16		**b**: 88
14		**c**:	0.1/ 4.3		**c**: 81
15		**e**:	0.2/ 16		**e**: 99
16	**9**	**f**:	0.2/ 9	**14**	**f**: 78
17		**4a**:	0.4/ 2.5		**15a**: 95
18		**b**:	0.8/13.5		**b**: 90
19		**e**:	0.4/ 5		**e**: 56
	10			**15**	

4a: $(CH_2O)_n$, **b**: R=C_9H_{19}, **c**: R=$(CH_2)_4$OTHP, **d**: R=$(CH_2)_4$OTBDMS, **e**: R=C_6H_4-*p*-OMe,
f: 

a: Yield is based on pyrone or coumarin derivatives.

Scheme 2. Synthesis of bisnorhelipyrone



Reagents and conditions: i, NaH, n-BuLi, acetaldehyde, 51%; ii, Jones reagent, 68%; iii, DBU, benzene, 54%; iv, DBU (0.4 eq), $(CH_2O)_n$, rt, 15 h, 99%.

In conclusion, we have clearly established that substituted methylenebis(4-hydroxy-2-pyrone) or methylenebis(4-hydroxycoumarin) derivatives (**5**) can be conveniently prepared from their respective parent compounds through DBU assisted solid state reaction with corresponding aldehydes (**4**) in satisfactory yields. The reaction is more general and complementary to the previously reported Et_2AlCl assisted condensation,[7] and would be helpful towards acid sensitive or less reactive electron rich aldehydes.

ACKNOWLEDGMENTS

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