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A New Preparative Method of 2,2-Dimethyl-2*H*-chromenes

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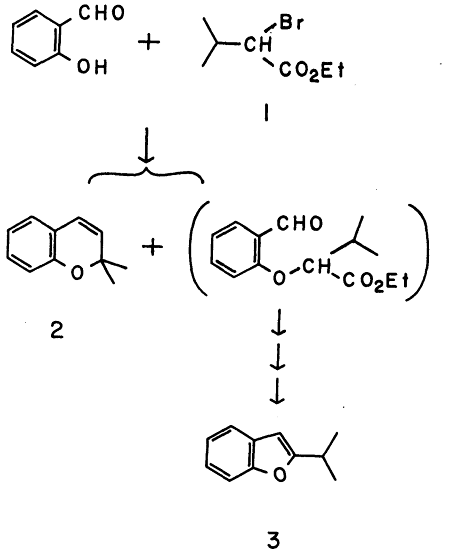
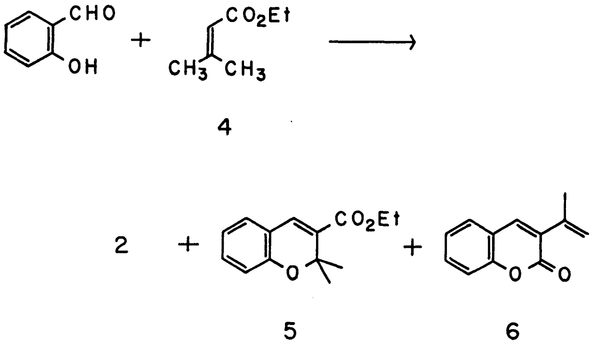
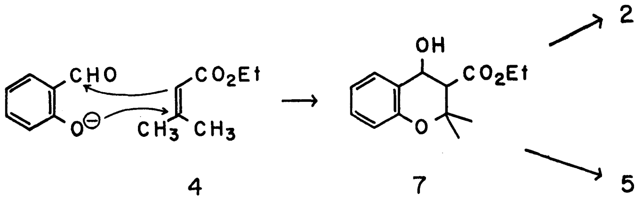
2,2-Dimethyl-2*H*-chromene was prepared from salicylaldehyde and ethyl 3-methyl-2-butenoate (or ethyl α-bromoisobutyrate) in one step. This new method of preparing 2,2-dimethyl-2*H*-chromene was studied and applied to some 2,2-dimethyl-2*H*-chromene derivatives.

Many methods to prepare 2,2-dimethyl-2*H*-chromenes have been reported,[1] but they have involved many reaction steps and low yields. In our preparative study of 2-isopropylbenzofuran, we found a new method to prepare 2,2-dimethyl-2*H*-chromenes. In this paper, we will report this new method.

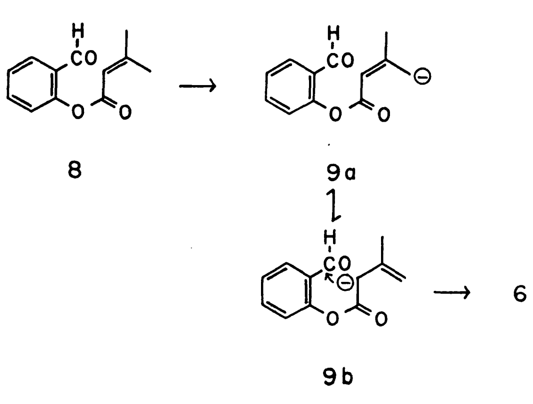


In general, 2-alkylbenzofurans are prepared from salicylaldehyde and ethyl α-bromocarboxylate.[2] In our preparative study of 2-isopropylbenzofuran (**3**) by this method, a solution of salicylaldehyde and ethyl α-bromoisobutyrate (**1**) in DMF was heated at 130 °C in the presence of potassium carbonate, and the products were distilled under reduced pressure. Moreover, the non-volatile part gave the expected 2-isopropylbenzofuran (**3**) after treatment with a 30% aqueous potassium hydroxide solution and sodium acetate-acetic anhydride. The volatile part consisted mainly of 2,2-dimethyl-2*H*-chromene (**2**). It was of great interest that 2,2-dimethyl-2*H*-chromene (**2**) was obtained in a one-step reaction. Next, the reaction of salicylaldehyde and ethyl α-bromoisobutyrate (**1**) was examined under several conditions. The results are given in Table 1. The reactions in DMF or in DMSO gave 2,2-dimethyl-2*H*-chromene (**2**), but those in THF or in pyridine did not. Also, satisfactory yields were obtained after 8 h both in DMF and in DMSO.





This reaction is thought to proceed as follows. Ethyl α-bromoisobutyrate (**1**) is converted to ethyl 3-methyl-2-butenoate (**4**) by dehydrobromination. Then, the phenolate ion attacks the C=C double bond in ethyl 3-methyl-2-butenoate (**4**), and the resulting carbanion attacks the C=O double bond in salicylaldehyde. These two nucleophilic attacks form ethyl 4-hydroxy-2,2-dimethylchroman-3-carboxylate (**7**) as an intermediate, which then readily loses ethanol and carbon dioxide to give 2,2-dimethyl-2*H*-chromene (**2**).



Next, the reaction of salicylaldehyde and ethyl 3-methyl-2-butenoate (**4**) was also examined under similar conditions; the results are given in Table 2. The yield of 2,2-dimethyl-2*H*-chromene (**2**) was the best at 8 h in this reaction. In several cases, 3-isopropenylcoumarin (**6**) was obtained. This new coumarin is thought to be formed as follows: The phenolate ion

TABLE 1. THE REACTIONS OF SALICYLALDEHYDE AND ETHYL α-BROMOISOBUTYRATE (**1**)

Solvent	Temp/°C	Time/h	Yield of **2**/%
DMF	130	5	3
		8	25
		16	29
DMSO	130	8	24
THF	Reflux	8	0
Pyr.	Reflux	8	0

TABLE 2. THE REACTIONS OF SALICYLALDEHYDE AND ETHYL 3-METHYL-2-BUTENOATE (**4**)

Base	Time/h	Yield/%		
		2	**5**	**6**
K_2CO_3	5	17	0	0
	8	35	1	3
	15	32	0	1
NaOEt	8	0	0	7
DBU	8	0	0	2

Solvent: DMF, temp: 130 °C.

attacks the C=O double bond in ethyl 3-methyl-2-butenoate (**4**) to give *o*-formylphenyl 3-methyl-2-butenoate (**8**), which loses the γ proton in 3-methyl-2-butenoate (**8**) to give the mesomery of the γ carbanion (**9a**) and the α carbanion (**9b**). Then, the α carbanion attacks the C=O double bond in the aldehyde to form 3-isopropenylcoumarin (**6**). Ethyl 2,2-dimethyl-2*H*-chromene-3-carboxylate (**5**) was also obtained. This ester is thought to be formed by the dehydration of ethyl 2,2-dimethyl-4-hydroxychroman-3-carboxylate (**7**).

This new method was applied to various salicylaldehydes, and some of them gave the corresponding 2,2-dimethyl-2*H*-chromene derivatives. All the reactions were carried out in DMF at 130 °C, for 8 h or 15 h. The results are given in Table 3. Methoxy-, methyl-, chloro-, bromo-, and phenyl-substituted salicylaldehydes gave the corresponding chromenes in good yields, but the others produced poor yields or nothing at all. This showed that this reaction was useful only for the preparation of 2,2-dimethyl-2*H*-chromenes with electrodonating or less electroaccepting substituents. Also, it was strange that 4-hydroxysalicylaldehyde and 2,4-dihydroxybenzaldehyde gave no corresponding chromene.

TABLE 3. THE REACTIONS OF SUBSTITUTED SALICYLALDEHYDES AND ETHYL 3-METHYL-2-BUTENOATE (**4**)

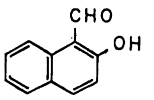
Substituted salicylaldehyde	Corresponding chromene	
	Bp θ_b/°C(mmHg)	Yield/%
3-Methoxy-	121—122 (7)	27*
4-Methoxy-	135—146 (8)	25
5-Methoxy-	141—144 (8)	47
6-Methoxy-	118—120 (16)	57
4,5-Dimethoxy-	155—160 (9)	22
4,6-Dimethoxy-	151—157 (9)	31
3-Methyl-	111—113 (24)	44
4-Methyl-	112—113 (21)	42
5-Methyl-	105—108 (21)	35
6-Methyl-	113—117 (14)	42
3-Chloro-	92—94 (9)	3, 5*
4-Chloro-	97—98 (5)	30
5-Chloro-	118—119 (29)	18, 32*
5-Bromo-	143—146 (19)	27
5-Phenyl-	53—55[a)]	35
5-Nitro-	……	0
6-Nitro-	100—105 (18)	2
4-Hydroxy-	……	0
5-Ethoxy carbonyl-	……	0
5-Acetyl-6-hydroxy-	……	0
A[b)]	……	0
B[b)]	……	0
C[b)]	……	0

Solvent: DMF, temp: 130 °C, time: 8 h (*15 h).

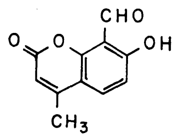
a) Mp θ_m/°C (recrystallized from ethanol).

b)

A



B



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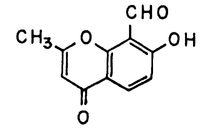

In two cases, the isopropenylcoumarins were also obtained. These two methyl substituted isopropenylcoumarins showed spectra similar to those of 3-isopropenylcoumarin (**6**) (Table 4). Their structures were confirmed by the partial catalytic hydrogenation of 3-isopropenyl-5-methylcoumarin to 3-isopropyl-5-methylcoumarin, which showed a doublet signal (J=7 Hz) at 1.3 ppm in its ^{1}H-NMR spectrum (Table 4).

TABLE 4. THE DATA ON NEW COUMARINS

Substituted coumarin	Mp θ_m/°C	Yield %	IR ν/cm^{-1}	^{1}H-NMR (δ)
3-Isopropenyl-	96.5—97.5	3	1725	2.1(3H,s),5.3(1H,s),5.9(1H,s), 7.0—7.7(4H,m),7.6(1H,s),
3-Isopropenyl-5-methyl-	65—67	6	1725	2.1(3H,s),2.5(3H,s),5.2(1H,s), 5.8(1H,s),6.8—7.2(2H,m), 7.2(1H,dd,J=7+9Hz),7.7(1H,s),
3-Isopropenyl-7-methyl-	65—72	Trace	1710	2.1(3H,s),2.5(3H,s),5.2(1H,s), 5.8(1H,s),7.0—7.2(2H,m), 7.3(1H,d,J=8Hz),7.5(1H,s),
3-Isopropyl-5-methyl-	87—91	—	1720	1.3(6H,d,J=7Hz),2.5(3H,s), 3.0(1H,m,J=7Hz),6.8—7.1(2H,m), 7.1(1H,dd,J=7+8Hz),7.5(1H,s),

Experimental

The boiling points and melting points have not been corrected; the IR spectra were measured on a Hitachi EPI-S2 spectrophotometer, and the ^{1}H-NMR spectra, on a JEOL JNM-MH-60 spectrometer in a carbon tetrachloride solution.

The Reaction of Salicyladehyde and Ethyl α-Bromoisobutyrate (1). A mixture of salicyladehyde (0.1 mol), ethyl 3-bromoisobutyrate (0.1 mol), potassium carbonate (40 g), and the solvent (shown in Table 1) (150 ml) was heated at 130 °C for the time shown in Table 1. After the removal of the solvent and ethyl 3-methyl-2-butenoate (**4**) *in vacuo*, the dark reaction mixture was diluted with water and extracted with ether. The ether solution was washed with 10% hydrochloric acid and a 5% aqueous sodium hydroxide solution, and then dried over anhydrous sodium sulfate. After the removal of the ether, the resulting liquid was distilled. 2,2-Dimethyl-2*H*-chromene (**2**) was thus obtained as a 106—108 °C/29 mmHg† fraction; the yield are summarized in Table 1. The residue was mixed with a 30% aqueous potassium hydroxide solution and refluxed for 3 h with stirring. After cooling, the mixture was treated with water and washed with ether. The aqueous layer was acidified with 10% hydrochloric acid and extracted with ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. After the removal of the ether, the resulting liquid was mixed with a mixture of anhydrous sodium acetate (12 g) and acetic anhydride (18 g). The mixture was then refluxed for 3 h. Still hot, the reaction mixture was poured onto 70 g of ice and extracted with ether. The ether solution was washed with saturated sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate. After the removal of the ether, the resulting liquid was distilled. 2-Isopropylbenzofuran (**3**) was thus obtained as a 111—113 °C/20 mmHg fraction; yield: 7% (8 h).

The Reaction of Salicylaldehyde and Ethyl 3-Methyl-2-butenoate (4). A mixture of salicylaldehyde (0.1 mol), ethyl 3-methyl-2-butenoate (**4**) (0.1 mol), anhydrous potassium carbonate (40 g), and DMF (80 ml) was heated at 130 °C for the time shown in Table 2. After the removal of the solvent and the recovered ethyl 3-methyl-2-butenoate (**4**) *in vacuo*, the dark reaction mixture was diluted with water and extracted with ether. The ether solution was washed with 10% hydrochloric acid and a 5% aqueous sodium hydroxide solution, and then dried over anhydrous sodium sulfate. After the removal of the ether, the resulting liquid was distilled. A fraction of 2,2-dimethyl-2*H*-chromene (**2**), boiling at 106—108 °C/29 mmHg, was then collected. The residue was chromatographed by the use of a silica-gel column with benzene–hexane (1 : 4) to afford ethyl 2,2-dimethyl-2*H*-chromene-3-carboxylate (**5**); bp 185—200 °C/18 mmHg; mp 43—45 °C; IR: 1710 cm^{-1}; ^{1}H-NMR: 1.3 (3H, t, J=7 Hz), 1.6 (6H, s), 4.2 (2H, q, J=7 Hz), 6.5—7.3 (4H, m), 7.2 ppm (1H, s); and 3-isopropenylcoumarin (**6**); mp 96.5—97.5 °C (recrystallized from hexane). The yields are summarized in Table 2, while the spectral data of **6** are sumarized in Table 4.

The General Procedure for the Preparation of Chromenes. A mixture of salicylaldehyde (0.1 mol), ethyl 3-methyl-2-butenoate (**4**) (0.1 mol), anhydrous potassium carbonate (40 g), and DMF (80 ml) was heated at 130 °C for 8 or 15 h. After treatment similar to that described above, the corresponding chromenes were obtained. Their data are summarized in Table 3. Two methyl isopropenylcoumarins were also obtained as white crystals (recrystallized from hexane); their data are summarized in Table 4.

Partial Hydrogenation of 3-Isopropenyl-5-methylcoumarin. 3-Isopropenyl-5-methylcoumarin (151 mg) was dissolved in 50 ml of ethanol, and then mixture was hydrogenated by means of a Raney Ni catalysts (prepared from 1 g of 50% Al–Ni alloy). After 30 m, about 23 ml of hydrogen absorbed. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure and extracted with ether. The ether solution was dried over anhydrous sodium sulfate. After the removal of the ether, 3-isopropyl-5-methylcoumarin (114 mg; 75%) was obtained as white crystals; mp 87—91 °C (recrystallized from hexane).

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† 1 mmHg≈133.322 Pa.

References

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2) T. Abe and R. Shimizu, *Nippon Kagaku Zasshi*, **91**, 753 (1970).