Alkylation of Hydroxypyrones

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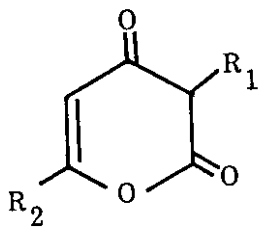
Summary: A procedure for the alkylation of hydroxypyrones with alkyl halides in the presence of potassium hydroxide in dimethyl sulphoxide (DMSO) at ambient temperature has been described. The method supercedes in simplicity and efficiency to those previously reported. The alkylation has been found to be very effective especially with methyl or ethyl iodide or benzyl bromide. To prove the general applicability of the method some related 4-hydroxycoumarins have also been alkylated.

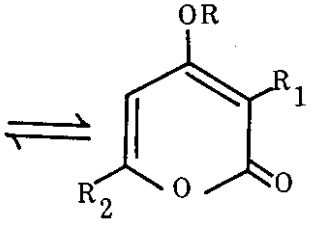
A number of methods have been reported for the alkylation of hydroxypyrones (1) using a variety of reagents. These include the use of diazomethane for the methylation of triacetic lactone [1-3] (1a), 6-phenylpyran-2,4-dione [1] (1d), 3,5-dialkylpyronone [4], yangonin [5] and aureothin [6] which results in the formation of 4-alkoxy-2-pyrones of type (II) as the predominant product along with a minor quantity of 2-alkoxy-4-pyrone of type (III). The reaction of silver salt [7] of hydroxypyrone with alkyl iodide or action of dimethyl sulphate [3,7] with hydroxypyrones in the presnece of potassium carbonate in ketone as solvent or action of 10% methanolic hydrochloric acid has been reported to give 4-alkoxy-2-pyrones of type (II). C-Methylations [8,9] at the 3-acetyl and 6-methyl positions in dehydroacetic acid (1e) and at 5- and 6-methyl positions of triacetic lactone (1a) have been effected with methyl halide in the presence of sodium amide in liquid ammonia. Recently the conversion of triacetic lactone (1a) have been effected with methyl halide in the presence of sodium amide in liquid ammonia. Recently the conversion of triacetic lactone (1a) to 2-methoxy-6-methyl-pyran-4-one (III) using methyl fluorosulphonate [10] and triethyl oxonium tetrafluoroborate or trimethyl oxonium tetrafluoroborate [11] or dimethoxy carbonium tetraluoroborate has been carried out. All these methods are time consuming, require special reagents and precautions against the ingress of atmospheric moisture. In view of the synthetic importance [12,13] and the occurrence of the alkoxypyrones in natural products [1,3] we were interested in evolving a simple and rapid method for the alkylation of hydroxypyrones. More recently reported methods [14,15] for N-alkylation (indole, pyrrole and amides) and O-alkylation [15] (phenol and carboxylic acids) using alkyl halide in the presence of potassium hydroxide or dimsyl sodium in dimethyl sulphoxide indicated the feasibility of alkylation of hydroxypyrones by an analogous method. The alkylation of a number of hydroxypyrones (1) with alkyl halides in the presence of potassium hydroxide in dimethyl sulphoxide at ambient temperature has been carried out and the results obtained are described in this paper.

Initial studies using anhydrous sodium carbonate in dimethyl sul-



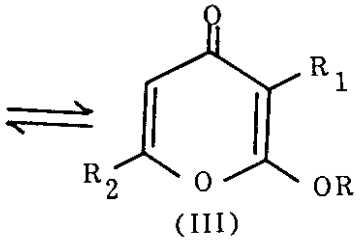
(I)

	R_1	R_2
a	H	Me
b	Br	Me
c	NO_2	Me
d	H	Ph
e	COMe	Me
f	COPh	Ph



(II)

	R	R_1	R_2
a	Me	H	Me
b	Et	H	Me
c	CH_2Ph	H	Me
d	Me	Br	Me
e	Me	NO_2	Me
f	Me	H	Ph
g	Me	COMe	Me
h	Et	COMe	Me
i	CH_2Ph	COMe	Me
j	Me	COPh	Ph
k	Et	COPh	Ph



(III)

R	R_1	R_2
Me	H	Me

phoxide (DMSO) or dimethylformamide for the alkylation of hydroxypyrones (1) did not yield the desired products. However, a mixture of triacetic lactone (1a), methyl iodide, anhydrous sodium carbonate and DMSO on prolonged stirring at room temperature gave a poor yield of 4-methoxy-2-pyrone (IIa). In contrast to the result with anhydrous sodium carbonate, the addition of appropriate hydroxypyrone (1) and alkyl halide to DMSO containing solid potassium hydroxide, on stirring at ambient temperature (25-30°C) resulted in the formation of 4-alkoxy-2-pyrones (II) in good yields. The results obtained are given in the table. (See experimental).

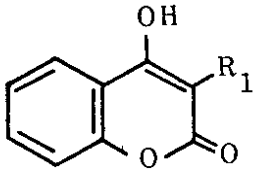
All reactions proceeded smoothly at room temperature and no special precautions were used to keep dry conditions. In almost all cases the methylation with methyl iodide was complete within 60 minutes, however in order to get maximum yield the reaction mixture was stirred for 70-75 minutes.

The rate of alkylation appears to be dependent on the nature of the alkyl halide. The reactions with methyl iodide occured more readily as compared to the reaction with ethyl iodide or benzyl bromide. Alkylation with long chain alkyl halide or branched chain alkyl halide was unsuccessful under these conditions. The addition of ter. alkyl halide to DMSO and KOH mixture initiated vigorous reaction with the evolution of gases which shows preferential dehydrochalogenation over alkylation. These findings are in agreement with the observations [14] recorded in the alkylation of indole and pyrrole with DMSO and potassium hydroxide.

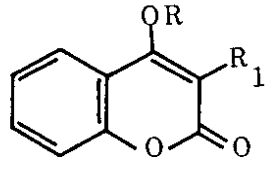
In the methylation of hydroxypyrones (using sodamide in liquid ammonia) and amide (in DMSO and KOH) C-methylation has also been reported, [9,15] the formation of such products has not been encountered in the alkylation of hydroxypyrone by the present method, although the compound (1e)

has a potential site for C-methylation at the 3-position.

The hydroxypyrones (1) can exist in tautomeric forms (1) and (III), therefore two types of alkylation products are possible. However, the alkylation results of our investigation indicate the formation of only 4-alkoxy-2-pyrones of type (II). The dominance [6,16] of a particular tautomeric form has been attributed to the solvent, temperature, nature of substituents, and pH of the medium. Presumably under our experimental conditions the hydroxypyrones (1) predominantly exist in 2-pyrone forms (II), hence the 2-alkoxyderivatives of type (III) are not formed.



(IV)



(V)

	R_1
a	H
b	NO_2
C	Br

	R	R_1
a	Me	H
b	Me	NO_2
c	Et	NO_2
d	$PhCH_2$	NO_2
e	Me	Br

The pyrone rings are susceptible to hydrolysis by bases. In the present investigation a strong base has been used but in no case the scission of pyrone ring has been observed. This is due to the fact that the solubility of potassium hydroxide in DMSO is very limited and the reaction proceeds only on the surface of the solid potassium hydroxide similar to the methylation of phenolic group with dimethyl suphate in the presence of solid potassium carbonate or potassium bicarbonate [17] and the esterification of carbolyc group with ethyl iodide in the presence of silver oxide [18].

In order to test the general applicability of the method some other related hydroxypyrones such as 4-hydroxycoumarin (IVa) and its derivative (IVb,c) have been alkylated to corresponding 4-alkoxyderivatives (V).

The results of the present investigation show that method offers an excellent synthetic alternative to the previously reported methods which are time consuming and require special reagents and dry conditions.

Experimental

Dehydroacetic acid (1e) used was from Koch-Light m.p. 110°C, triacetic lactone [19] (1a), 3-bromotriacetic lactone [20] (1b), 3-nitrotriacetic lactone [20] (1c), dehydrobenzoylacetic acid [21] (1f), 4-hydroxy-6-phenylpyran-2-one [22] (1d), 4-hydroxycoumarin [23] (IVa), 4-hydroxy-6-phenylpyran-2-one [22] (1d), 4-hydroxycoumarin [23] (IVa), 4-hydroxy-3-nitrocoumarin [23] (IVb) and 3-bromo-4-hydroxycoumarin [24] (IVc) were prepared by the methods given in literature.

General method used for the alkylation of hydroxypyrones (1)

To a mixture of powdered potassium hydroxide (0.004 mol) in dimethyl sulphoxide (5-7ml) was added the appropriate alkyl halide (0.002 mol) and hydroxypyrone (0.001 mol) with stirring at room temperature (23-30°C). The reaction mixture was stirred at room temperature for different periods of time and then filtered. The residue washed with 1-2 ml of dimethyl sulpho-

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Hydroxypyrone	Alkyl halide	Product m.p.(lit.m.p.)	Yield %	Time(Minutes)
1a	MeI	11a 87°C(87.5-88.5°C) [1]	70	70 - 75
1a	EtI	11b 59°C(58-60°C) [7]	50	80
1a	$PhCH_2Br$	IIc 92°C(92°C) [25]	50	90
1b	MeI	IId 153°C(155°C) [20]	60	70 - 75
1c	MeI	IIe 167°C(165-167°C)[20]	60	75
1d	MeI	IIf 128-130°C(129.5-131.5°C)	65	75
1e	MeI	IIg 93°C(91°C) [26]	60	75
1e	EtI	IIh 94°C(93-95°C) [27]	55	90
1e	$PhCH_2Br$	IIi 94°C(94-95°C) [25]	54	85
1f	MeI	iij 137-138°C	80	75
1f	EtI	IIk 159°C	70	90
IVa	MeI	Va 125°C (125°C) [24]	65	75
IVb	MeI	Vb 98-99°C) [28]	65	75
IVb	EtI	Vc 140°C(140°C) [28]	60	90
IVb	$PhCH_2Br$	Vs 142° (142°-143°C) [28]	50	75-80
IVc	MeI	Vd 90°C (90-91°C) [24]	60	75

xide. The filtrate was added to water (20-25 ml) and acidified with dilute hydrochloric acid (pH 5-6). The solid product if any was filtered out and filtrate extracted with chloroform (3 x 10 ml) which on evaporation gave an additional quantity of the product. In those cases where no solid product was obtained on acidification, the solution was extracted with chloroform (3 x 10 ml), dried over calcium chloride and evaporated under reduced pressure. The results obtained are given in the table.

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