PHASE-TRANSFER CATALYSED ALKYLATION OF 3-HYDROXYCOUMARIN

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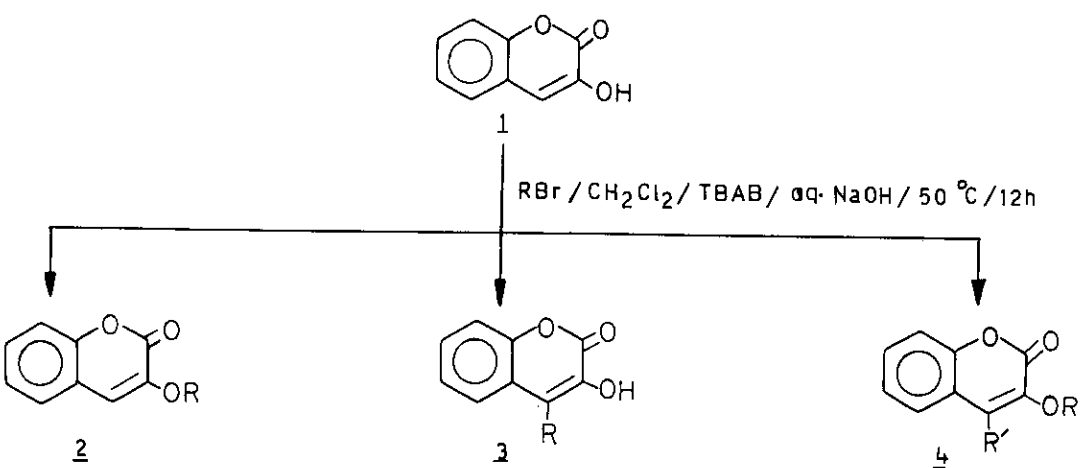
Abstract - Phase-transfer catalysed alkylation of 3-hydroxycoumarin with active alkyl halides gave O-alkylated products (45-60%), C-alkylated products (20-40%) and in one case C,O-dialkylated product (20%).

In the course of our studies on the synthesis of 3-4 fused furano- and pyranocoumarins[1] we had to prepare a number of allylic and acetylenic ethers of 3-hydroxy- and 4-hydroxycoumarins and normal procedure was followed for these alkylation in acetone/potassium carbonate - a versatile alkylating medium. In recent years phase-transfer catalysis has been proved to be a superior alternative with more advantages as well as greater successes and a number of ethers of both simple and highly hindered phenols have been prepared[2] by McKillop and coworkers. Although sufficiently explored, interesting results[3] are still observed with phase-transfer catalysed procedures particularly with systems containing ambident nucleophilic sites. 3-Alkyl- and 4-alkylcoumarins constitute an important class of compounds having interesting physiological activities[4] and extensive work has been done on the synthesis of these classes of compounds[5]. We considered a possibility of their synthesis involving the alkylation utilising the O/C nucleophilic sites in the corresponding tautomeric hydroxycoumarins.

Recently we have demonstrated the preferential C-alkylation in the phase-transfer catalysed alkylation[3a] of the anthrone-anthranol system with different active alkyl halides. Herein, we report the results of phase-transfer catalysed alkylation of 3-hydroxycoumarin with a number of active alkyl halides (**Scheme 1**).

When a two phase mixture of 3-hydroxycoumarin (**1**) (6 mmol), benzyl bromide (12 mmol),dichloromethane (50 ml) and 1% aqueous sodium hydroxide (50 ml) solution was heated on a water bath at 50°C in presence of tetrabutylammonium bromide (TBAB), the starting 3-hydroxycoumarin disappeared after 12 h. The reaction mixture after suitable work-up gave 3-benzyloxycoumarin (**2a**) in 60% yield. With allyl bromide under identical stoichiometric composition and reaction conditions, a mixture of two products was obtained. These on subsequent chromatographic separation over silica gel affored 3-allyloxycoumarin[6] (**2b**, 56%) and 4-allyl-3-hydroxycoumarin[6] (**3b**, 20%). Crotyl bromide also reacted in a similar fashion and both the O-alkylated product (**2c**, 55%) and the rearranged **3c** (30%) by SN_2' substitution were obtained. Amount of C-alkylation (40%) increased slightly when prenyl bromide was used as the alkylating agent and this time also the predominant product was 3-prenyloxycoumarin (**2d**,45%).

The nature of alkylation viz. C- and O- in these products (**2a-d, 3b-d**) was determined from the presence or absence of ν_{O-H} in their ir spectra together with the absence or presence of the C-4 proton at ~ δ 6.8 in their ^{1}H-nmr spectra. The C-alkylated products (**3b-d**) lacked the C-4 proton in



Scheme 1

^{1}H-nmr spectra but showed the presence of ν_{O-H} at 3360 cm^{-1} in their ir spectra. On the other hand, all the O-alkylated products showed the presence of C-4 proton in their ^{1}H-nmr spectra and absence of ν_{O-H} in their ir spectra. Other physical and spectroscopic data of all the compounds are provided in **Table 1**.

With propargyl bromide again a mixture of two products was obtained. One of these was found to be identical with our earlier obtained 3-propargyloxycoumarin[1b] in all respect viz. mp, tlc and superimposable ir while the other (**4e**) lacked both ν_{O-H} in the ir spectrum and C-4 proton in its ^{1}H-nmr spectrum indicating C,O-dialkylation. The product was characterised as 4-allenyl-3-propargyloxycoumarin from its ^{1}H-nmr and mass spectra. Similar isomerisation of $-CH_2-C\equiv CH$ to $-CH=C=CH_2$ in basic medium is well-known in literature[7] and even during phase-transfer catalysed condition is also not unprecedented. In fact this has led to the valuable synthesis of N-propadienylacridone[8]. Inspite of our repeated attempts the tertiary halides 3-chloro-3-methylbut-1-yne and 3-bromo-3-methylbut-1-ene failed to react with 3-hydroxycoumarin under similar conditions.

Table 1. Physical data of compounds (**2a-2d,3b-3d & 4e**)

Compound	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	Analysis(%) Calculated C	Calculated H	Found C	Found H	uv(MeOH) λ_{max}(nm)[d]	ir(KBr) $\nu(cm^{-1})$[e]	^{1}H-nmr($CDCl_3$) δ, J=Hz[f]
2a	60	156	$C_{16}H_{12}O_3$	76.19	4.76	76.45	4.65	245,290, 310	1720,(C=O)	5.16(s,2H),6.86(s,1H),7.20-7.64(m, 9H)
2b	56	95	$C_{12}H_{10}O_3$	71.28	4.95	71.05	5.10	245,290, 310	1720,(C=O)	4.60(d,2H,J=5.5),5.30-5.40(m,2H), 6.00-6.10(m,1H),6.85(s,1H),7.00-7.40(m,4H)
2c	55	95	$C_{13}H_{12}O_3$	72.22	5.55	71.95	5.70	245,290, 310	1720,(C=O)	1.75(d,3H,J=6),4.48-4.80(m,2H), 5.56-6.12(m,2H),6.82(s,1H),7.20-7.60 (m,4H)
2d	45	142	$C_{14}H_{14}O_3$	73.04	6.08	73.15	6.15	245,292, 310	1715,(C=O)	1.64(s,6H),4.92-5.16(m,2H),6.08-6.36(m,1H),6.80(s,1H),7.12-7.36 (m,3H),7.92-8.00(m.1H)
3b	20	148	$C_{12}H_{10}O_3$	71.28	4.95	71.15	4.85	248,310	1710,(C=O) 3360,(OH)	3.52-3.68(m,2H),5.04-5.32(m,2H), 5.68-6.20(m,1H),6.36(s,1H),7.20-7.68(m,4H)
3c	30	110	$C_{13}H_{12}O_3$	72.22	5.55	72.15	5.60	248,310	1700,(C=O) 3360,(OH)	1.56(d,3H,J=8.0),4.00-4.40(m,1H), 5.08-5.32(m,2H),6.08-6.40(m,1H), 6.42(s,1H),7.20-7.40(m,3H),7.72-7.88(m,1H)
3d	40	120	$C_{14}H_{14}O_3$	73.04	6.08	72.95	6.20	248,310	1710,(C=O) 3360,(OH)	1.68(s,3H),1.80(s,3H),3.56(d,2H, J=6.5),5.04-5.28(m,1H),6.32(s,1H), 7.20-7.64(m,4H)
4e	20	110	$C_{15}H_{10}O_3$	75.63	4.20	75.55	4.25	248,290	1710,(C=O) 1950,(C=C=CH_2) 2135,(C≡CH)	2.48(t,1H,J=2.5),5.00(d,2H,J=2.5), 5.22(d,2H,J=7.0),6.70(t,1H,J=7.0), 7.20-7.60(m,3H),8.08-8.24(m,1H)

[a]Yield of pure isolated product. [b]Recorded on H_2SO_4 bath and are uncorrected. [c]Microanalyses obtained from CDRI, Lucknow. [d]Recorded on a Hitachi 200-20 spectrophotometer. [e]Recorded on a Perkin-Elmer 1330 infrared spectrophotometer. [f]Recorded on a Jeol Fx-100 NMR spectrometer at IICB, Calcutta.

EXPERIMENTAL

Alkylation of 3-Hydroxycoumarin, General Procedure : To a mixture of 3-hydroxycoumarin 1(1.0g,6mmol) and alkyl halide (RBr,12 mmol) in CH_2Cl_2(50 ml) is added a solution of TBAB (0.08g, 0.25 mmol) in 1% NaOH (50 ml) and the mixture is heated on water bath at 50°C for 12 h. The organic layer is washed successively with 2N HCl (3 x 50 ml), brine (3 x 50 ml) and dried (Na_2SO_4). The solvent is removed and the residual mass is chromatographed over silica gel (SRL, 60-120 mesh). The compounds are obtained when the column is eluted with the following solvent/sovents : benzene/petroleum ether (60-80°), 1:1 (**2a**), 1:1 (**2b**), 1:1 (**2c**); benzene/petroleum ether (60-80°), 1:3 (**2d**); benzene (**2e**); benzene/petroleum ether (60-80°), 1:3 (**3b**); benzene/petroleum ether (60-80°), 1:9 (**3c**), 1:9 (**3d**); benzene/petroleum ether (60-80°), 1:3 (**4e**).

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