

PHASE-TRANSFER CATALYSED ALKYLATION OF 3-HYDROXYCOUMARIN

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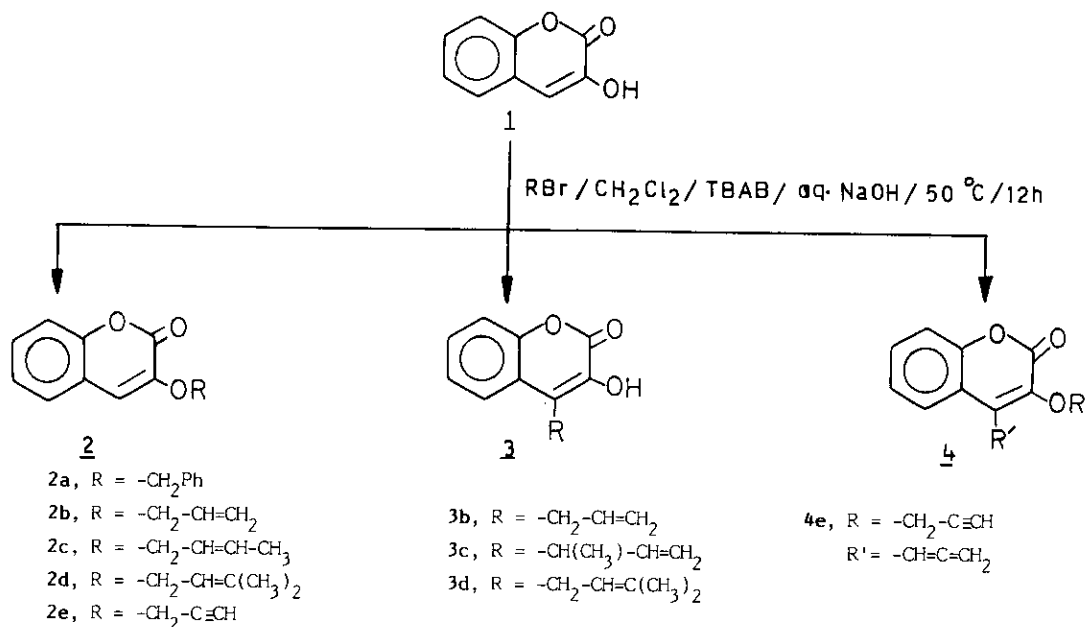
Abstract - Phase-transfer catalysed alkylation of 3-hydroxycoumarin with active alkyl halides gave O-alkylated products (45-60%), C-alkylated products (20-40%) and in one case C,O-dialkylated product (20%).

In the course of our studies on the synthesis of 3-4 fused furano- and pyranocoumarins¹ 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 prepared² by McKillop and coworkers. Although sufficiently explored, interesting results³ 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 activities⁴ and extensive work has been done on the synthesis of these classes of compounds⁵. 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-benzyloxy coumarin (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 afforded 3-allyloxy coumarin⁶ (2b, 56%) and 4-allyl-3-hydroxycoumarin⁶ (3b, 20%). Crotyl bromide also reacted in a similar fashion and both the O-alkylated product (2c, 55%) and the rearranged 3c (30%) by S_N2, 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-prenyloxy coumarin (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 $\nu_{\text{O-H}}$ in their ir spectra together with the absence or presence of the C-4 proton at $\delta 6.8$ in their $^1\text{H-nmr}$ spectra. The C-alkylated products (**3b-d**) lacked the C-4 proton in



Scheme 1

$^1\text{H-nmr}$ spectra but showed the presence of $\nu_{\text{O-H}}$ 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 $^1\text{H-nmr}$ spectra and absence of $\nu_{\text{O-H}}$ 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 $\nu_{\text{O-H}}$ in the ir spectrum and C-4 proton in its $^1\text{H-nmr}$ spectrum indicating C,O-dialkylation. The product was characterised as 4-allenyl-3-propargyloxycoumarin from its $^1\text{H-nmr}$ and mass spectra. Similar isomerisation of $-\text{CH}_2-\text{C}\equiv\text{CH}$ to $-\text{CH}=\text{C}=\text{CH}_2$ in basic medium is well-known in literature⁷ and even during phase-transfer catalysed condition is also not unprecedented. In fact this has led to the valuable synthesis of N-propadienylacridone⁸. In spite 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 (%)		uv(MeOH)		ir (KBr) ν(cm ⁻¹) ^e	¹ H-nmr (CDCl ₃) δ, J=Hz ^f
				Calculated C H	Found C H	λ _{max} (nm) ^d	λ _{max} (nm) ^d		
2a	60	156	C ₁₆ H ₁₂ O ₃	76.19	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	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	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	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	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	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	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	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)

^aYield of pure isolated product. ^bRecorded on H₂O bath and are uncorrected. ^cMicroanalyses obtained from CDRI, Lucknow. ^dRecorded on a Hitachi 200-20 spectrophotometer. ^eRecorded on a Perkin-Elmer 1330 infrared spectrophotometer. ^fRecorded 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/solvents : 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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