

PRENYLATION OF HYDROXYBENZOPHENONES USING ACID (BF₃) AND BASE (Ag₂O) CATALYSTS

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ABSTRACT

Using 2-methylbut-3-ene-2-ol and BF₃-etherate as catalyst, 2, 4-dihydroxybenzophenone gives the 3-C-prenyl and 3, 5-di-C-prenylated compounds. With 2, 4, 4'-trihydroxybenzophenone, the products are (i) 4, 4'-di-O-prenyl ether, (ii) a cyclised prenylated product involving condensation of two prenyl groups together and a minor, (iii) 5-C-prenylated product obtained in the form of its 2, 2-dimethylchroman. With Ag₂O as catalyst and using prenyl bromide, 4-hydroxybenzophenone gives its 3-C-prenylated product, which was not the case in K₂CO₃-acetone medium.

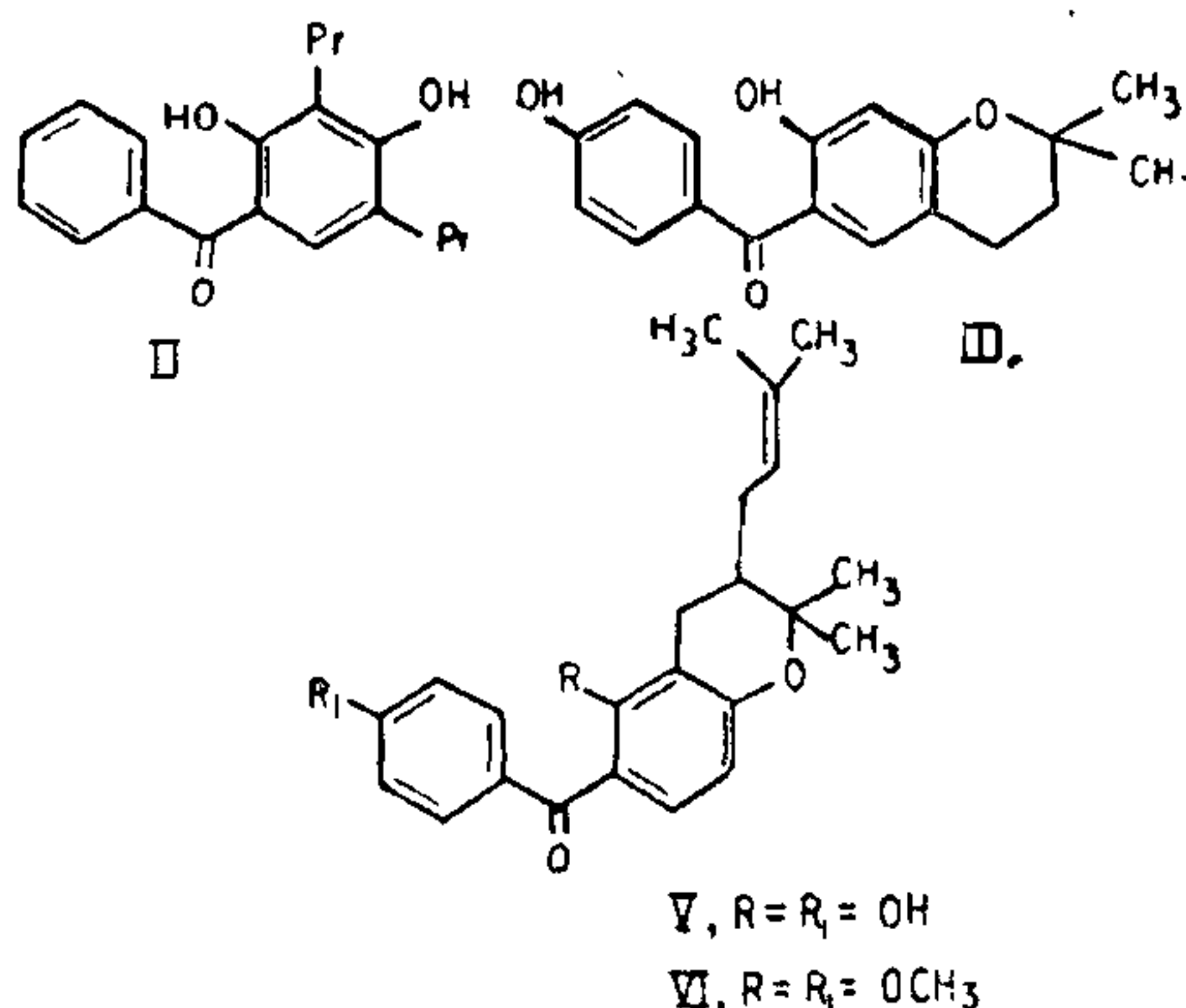
In earlier communications^{1,2}, prenylations of hydroxybenzophenones under weak and strong alkaline conditions have been reviewed at some length. The study also related to the effect of the side phenyl group in such reactions and on the strength of the chelation due to ortho and para hydroxyls respectively. The present work is the further extension of prenylation of hydroxybenzophenones, using acidic and basic catalysts.

As mentioned earlier¹, phenolic benzophenones are acyclic analogues of the appropriate xanthenes. Hence, it was thought worthwhile to use BF₃-etherate in the prenylation of 2, 4-dihydroxy and 2, 4, 4'-trihydroxybenzophenones, both having the resorcinol system.

2, 4-Dihydroxybenzophenone was treated with 2-methylbut-3-ene-2-ol in dioxane medium in the presence of BF₃-etherate. The reaction product after chromatographic separation gave two compounds, identified as 2, 4-dihydroxy-3-C-prenyl-(I, mp 120°, lit.¹ mp 120–21°) and 2, 4-dihydroxy-3, 5-di-C-prenyl-(II, mp 74–75°) benzophenones. The latter substance was a new compound and its structure was established from analytical and spectral data.

Another reaction has been carried out with 2, 4, 4'-trihydroxybenzophenone using 2-methylbut-3-ene-2-ol and BF₃-etherate. From the alkaline and neutral fractions of the reaction product, three substances have been isolated. The alkaline fraction after acidification afforded 6-(4'-hydroxybenzoyl) 7-hydroxy-2, 2-dimethylchroman (III). The neutral ethereal fraction showed on TLC, spots for two compounds. Their separation was effected on a silica gel column and eluting with light petrol-benzene. The fast moving fraction provided 2-hydroxy-4,4'-diprenyloxybenzophenone (IV, mp 73–74°, lit.¹ mp 73°). The latter benzene eluates gave a substance (A), mp 82°, whose analytical data indicated the presence of two prenyl units in the benzophenone. From the NMR spectra, the presence of any of them being prenyloxy groups was ruled out. Further, a signal at δ 6.4 (d, J = 6 Hz)

indicated that there was an ortho coupled aromatic proton next to an alkoxy group. There was also a chelated -OH group signal. Of all the possibilities, the aliphatic protons of the two prenyl groups could best be accounted for by formulating the compound (A) as V. Traces of (A) were also found to be present in the Na₂CO₃ extract. The dimethyl ether of V was an oil, but its NMR spectrum also supported the formulation of the diprenylated product as VI.



Considering the enhanced nucleophilic reactivity of the 3- and/or 5-positions of 4-hydroxybenzophenone (as compared to 4-hydroxyacetophenone), a prenylation reaction has also been done using Ag₂O as catalyst. The reaction was done with equimolar quantities of the benzophenone and the prenyl bromide in dioxane-Ag₂O. The reaction product after chromatographic purification was identified as 4-hydroxy-3-C-prenylbenzophenone, mp 76–77° (lit.¹ mp 77°)

Following up the study with prenylation, the general features of the prenylation of two hydroxybenzophenones using BF₃-etherate, have been found to be the same as those reported for acetophenones³. But whereas in the case of β-resacetophenone, the yield of C-3 mono and C-3, 5-diprenylated products was small, in the case of 2, 4-dihydroxybenzophenone, the

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yield of C-3 and C-3, 5-prenylated products are fairly good. In the case of 2, 4, 4'-compound, no C-3 or C-3, 5-prenylated products were obtained but C-prenylation of a different type as mentioned in the case of β -resacetophenone³ seems to have taken place. There was some indication of a little 5-C-prenylation also, in the form of the chroman (III). The experiment with 4-hydroxybenzophenone shows Ag_2O to be more effective than acetone- K_2CO_3 for mild conditions of prenylation. Apart from Ag_2O being a basic oxide, influence of silver ions generated during the reaction may be one of the other reasons for its efficacy.

EXPERIMENTAL

2, 4-Dihydroxy-3-C-prenyl- and 2, 4-dihydroxy-3, 5-di-C-prenylbenzophenones (I and II):

2, 4-Dihydroxybenzophenone (2 g) was dissolved in dry dioxane (50 ml). To this solution was added BF_3 -etherate (0.5 ml), 2-methylbut-3-ene-2-ol (1.3 g) and the mixture stirred at 60–70° for 2 hr. The solution was cooled, extracted with ether and the ethereal solution washed with water, whereby the dark colour of the solution got discharged. The ethereal solution was dried (Na_2SO_4) and then the ether distilled off. The residue was subjected to column chromatography and elutions done successively with light petrol, light petrol-benzene and finally with pure benzene. The identity of the fast moving compound as 2, 4-dihydroxy-3-C-prenylbenzophenone (I, 70 mg) obtained from fraction (i) was established by comparison (mmp 120–21° and IR) with the authentic sample obtained earlier¹, in NaOMe - MeOH medium. Fraction (ii) obtained from the latter benzene eluates gave 2, 4-dihydroxy-3,5-di-C-prenylbenzophenone. After crystallisation from benzene-light petrol, it came out as yellow needles (II, 100 mg) mp 74–75°. Found: (C, 78.4, H, 7.4; $\text{C}_{23}\text{H}_{26}\text{O}_3$ requires C, 78.3, H, 7.4%); IR (KBr): 3300 (–OH), 2900 (– CH_3), 1650 ($>\text{C}=\text{O}$) cm^{-1} ; UV (MeOH): 355, 295, 265 nm. NMR (CDCl_3) δ : 1.8 [m, 12H, 2C(CH_3)₂], 3.3 and 3.5 [2d, 4H, two Ar. CH_2 - each having $J = 9\text{Hz}$], 5.3 [t, 2H, two vinylic protons (– $\text{CH}=\text{C}$)₂], 7.1 [s, H, 6-H], 7.2–7.5 [m, five H of the side phenyl ring] In the offset, presence of a chelated hydroxyl group was shown.

Reaction of 2, 4, 4'-trihydroxybenzophenone with 2-methylbut-3-ene-2-ol:

To a stirred solution of 2, 4, 4'-trihydroxybenzophenone (2 g) in dry dioxane (50 ml) was gradually added BF_3 -etherate (0.5 ml) and 2-methylbut-3-ene-2-ol (1.5 g). The whole solution was stirred for 3 hr at 50–60°. The solution was then cooled, extracted with ether and the ethereal solution given washings with water. It was then extracted with 5% aq. Na_2CO_3 . Acidification of this extract with dil. HCl provided a

solid which showed spots for two compounds on TLC (benzene). The faster moving compound on TLC was obtained by column chromatography (silica gel and benzene-5% ethyl acetate elutions). It came out as an oily mass, but gave a sharp single spot on TLC. IR (film): 3400 (–OH), 2900 (– CH_3), 1640 ($>\text{C}=\text{O}$) cm^{-1} ; UV (MeOH): 300, 330 nm.; NMR (CDCl_3) δ : 1.45 [s, 6H, C(CH_3)₂], 1.85 and 2.87 [2t, 4H of the chroman ring], 6.7 [s, H, 8-H], 7.2–7.9 [m, 5H, 5-H and four H of the side phenyl ring]. Presence of a chelated hydroxyl was shown in the offset.

The residue from the ethereal fraction remaining after Na_2CO_3 extraction was subjected to column chromatography (silica gel and successive elutions with light petrol and benzene). Practically nothing came from the light petroleum ether eluates. From the benzene eluates could be isolated a small amount (20 mg) of 2-hydroxy-4, 4'-diprenyloxybenzophenone, whose identity was established by comparison with the authentic sample¹ (mmp and co-IR). The latter benzene eluates gave the chroman (V) as an oil, which solidified after keeping in the vacuum desiccator for several days, mp 82–83° (light yellow needles from benzene-light petroleum ether), yield 200 mg. Found: (C, 74.9, H, 6.6; $\text{C}_{23}\text{H}_{26}\text{O}_4$ requires C, 75.4, H, 7.1%); IR (KBr): 3350 (–OH), 2900 (– CH_3), 1660 ($>\text{C}=\text{O}$) cm^{-1} . UV (MeOH): 294, 320 (inflection) nm.; NMR (CDCl_3) δ : 1.3 [d, 6H, C(CH_3)₂; of the chroman ring], 1.7 and 1.9 [2s, 6H, C(CH_3)₂ allylic methyls], 1.8–2.9 [m, aliphatic five H], 5.3 [t, H, – $\text{CH}=\text{C}$], 6.4 [ortho coupled aromatic proton at C-8, $J = 6\text{Hz}$], 7.0–7.6 [m, 5H, 7-H and four H of the side phenyl ring]. Methylation of the chroman (V) with excess of dimethyl sulphate in refluxing acetone- K_2CO_3 for 4 hr gave di-O-methyl ether as oil. Its NMR spectrum had signals for two methoxyl groups at δ 3.5. The rest of the signals were same as in the parent compound.

4-Hydroxy-3-C-prenylbenzophenone:

4-Hydroxybenzophenone (1 g), prenyl bromide (2 ml), dioxane (25 ml) and silver oxide (0.5 g) were stirred at room temperature for 2 hr. The solution was then filtered and the filtrate taken in ether. The ethereal solution was washed with water, dried (Na_2SO_4) and then the ether distilled off. The residue was purified over a silica gel column (benzene elution). The fast moving fraction yielded 4-hydroxy-3-C-prenylbenzophenone (mp. 76°, lit.¹ mp 76–77°), yield 175 mg. The latter benzene eluates gave only the starting material.

1. Mathur, A. K., Mathur, K. B. L. and Seshadri, T. R., *Indian J. Chem.*, 1977, 15B, 54.
2. —, *Ibid.*, 1977, 15B, 1065.
3. Bajwa, B. S., Lal, P. and Seshadri, T. R., *Tetrahedron Lett.*, 1972, 32, 3371–74 and the earlier references cited there.