33. Studies on Benzylation of Phenolic Hydroxyl Groups

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Our continuing effort in search of an efficient β -stimulant culminated in the discovery of 5, 7-dihydroxy-1-(3', 4', 5'-trimethoxybenzyl)-1, 2, 3, 4-tetrahydroisoquinoline (II) as a promising substitute for trimetoquinol-hydrochloride (I), which is now being used in the crinical fields as a β -stimulant, discovered in our laboratories more than a decade ago.¹⁾

The synthesis of (II) was started from ethyl 3,5-dihydroxy-benzoate (ethyl α -resorcylate) (III), which was converted first to the dibenzylether (IV), from which the final product (II) was obtained via several steps.

It is well known that resorcinol and some of its derivatives readily give O-benzylethers contaminated with O, C-poly-benzylated products. In our present case, however, we deemed the presence of ethoxycarbonyl group at meta-position of two hydroxyl groups would prevent C-benylation to give cleanly O, O-dibenzylether (IV).

Thus a mixture of compound (III) dissolved in ethanol or acetone, benzyl chloride and dry powdered potassium carbonate was refluxed and worked up according to the conventional method. Against our expectation the crude O, O-dibenzylether (IV) obtained was contaminated with O, C-poly-benzylated products, whose amount attained to a few per cent.

In order to minimize the formation of the by-product we carried out the benzylation experiments in various other solvents than the conventional alcohols and acetone, and found that acetonitrile (CH_3CN) is the best solvent for our purpose.

Thus when the benzylation was conducted in acetonitrile under otherwise the same working conditions, there was obtained crude O, O-dibenzylether (IV) in an excellent yield, with little sign of contamination by O, C-poly-benzylated by-product. Thus the crude product could be used directly in the next step. The yield of the purified product attained over 90%.

When the above experiment was carried out in the presence of 1/2.5 Mol-equiv. of 18-crown-6 the reaction was completed in 2 hr giving better yield of the product. Moreover the expensive crown ether

could be readily recovered and recycled without loss of activity, thus this seems to be the best method of preparation of (IV) applicable to a larger scale production for industrial purpose.

Salicylic aldehyde benzylether (VI), which is one of the starting materials of our work now is under way, was prepared about twenty years ago by Miyano *et al.*,²⁾ by treating the aldehyde (V) with benzyl bromide and potassium carbonate in acetone under reflux in a yield of ca. 75%. In our hands the above method using benzyl chloride in place of benzyl bromide gave a deep red solution*¹⁾ from which the benzyl ether was obtained in 30% yield.

When the benzylation experiment was carried out in acetonitrile under reflux for several hours no remarkable coloration of the reaction solution was observed and the benzyl ether was obtained in over 90% yield after one distillation in a pure enough quality applicable to the next stage. Though here again crown ether was effective in shortening the reaction time considerably, but in this case its recovery is so laborious that its use appears not profitable in industrial work.

Acetonitrile, low priced and easily recoverable, seems to be a solvent of choice for phenolic O-benylation and also for benzyl ester preparation (*vide infra*, experimental section).

Experimental. Ethyl α -resorcylate dibenzylether (IV). A mixture of ethyl α -resorcylate (1.82 g, 10 mM), dry K_2CO_3 -powder (2.76 g, 20 mM) benzyl chloride (3.1 g, 22 mM, 90% purity), 18-crown-6**¹⁾ (1.05 g, 4 mM, 1/2.5 eq.) and CH_3CN (30 ml) was refluxed gently in N_2 -atmosphere with stirring for 2 hrs. The solid was filtered off, washed with a small amount of CH_3CN . Combined CH_3CN -solution was evaporated (CH_3CN recovered) and the residue was dissolved in ether, filtered, evaporated. The oily residue was dissolved in minimum amount of hexane, allowed to stand in an ice-chest. The separated

*¹⁾ The deep coloration might have been caused by initial aldol-type condensation between aldehyde and acetone catalyzed by K_2CO_3 , followed by some complicated reactions. Thus in this case acetone seems not suitable as solvent.

**²⁾ Without crown-ether longer reaction time (8–10 hrs) was required for completion.

crystalline solid (2.92 g, yield 80.5% of the theoretical, m.p. 68–68.5°) is analytically pure. $C_{23}H_{22}O_4$ Calcd. C 76.22, H 6.12 Found C 76.12, H 6.25. IR and Mass spectral data were also satisfactory.

Recycle experiment of 18-crown-6: When the mother liquor of the first crop was evaporated, there remained pale yellow oil (1.34 g), which contains all the crown-ether used and recoverble O-benzylated ester. In stead of raising the second crop, this oily substance was used in the crown-ether recycle experiment, which was carried out exactly as mentioned above, except the recovered oil (1.34 g) was used in place of the crown-ether (1.05 g), yielding 3.55 g (98.1% yield) of the O-benzylated ester of m.p. 68–69°, identical with an authentic specimen obtained above.

Benzyl α -resorcyate dibenzylether: α -resorcylic acid (1.54 g, 10 mM), dry $KHCO_3$ -powder (3.0 g, 30 mM), benzyl chloride (4.64 g, 33 mM, 90% purity) and crown-ether (1.05 mM, 1/2.5 equiv.) were mixed together in CH_3CN (30 ml) and the whole was refluxed several hours with stirring in N_2 -atmosphere. Worked up as mentioned above, giving the crude objective product (3.76 g, 88.7%), m.p. 54.5–60°, raised to 57–60° once purified from n-hexane, which gave satisfactory combustion analysis data.

Salicylic aldehyde benzyl ether (VI): Aldehyde (V) (6.11 g, 0.05 M) was dissolved in CH_3CN (150 ml), to which dry K_2CO_3 -powder (6.91 g, 0.05 M) and benzyl chloride (6.96 g, 0.055 M) were added. The mixture was refluxed for 6 hrs in N_2 -atmosphere, giving a yellow solution. On cooling solid was removed by filtration and washed with CH_3CN . Solvent was removed from combined solution and the residue was distilled in vac., yielding 10.05 g of the benzyl ether (b.p._{0.3} 135–137°), y. 94.7%; gave correct combustion analysis data.

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References

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