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PHASE TRANSFER CATALYZED ACYLATION

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Summary: Sterically crowded phenols are conveniently acylated under phase transfer conditions. Selective 3-OH acylation of estradiol is accomplished by this method.

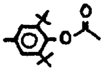
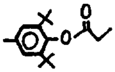
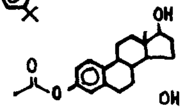
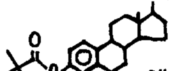
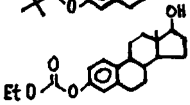
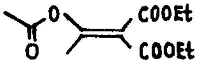
In contrast to the abundance of reports on phase transfer catalyzed (PTC) alkylation there are surprisingly few papers on this type of acylation[1,2,3]. The reason for this may lie in the common belief that it seems unreasonable to work with an acid chloride in an aqueous NaOH/organic solvent two-phase system.

In continuation of our work on the N-acylation of indole[4] we found PTC-acylation of phenols,anilines and active methylene compounds to be a very mild,short and high yield method of charming simplicity(see representative example). The use of a solid/liquid two-phase system consisting of powdered NaOH and an appropriate organic solvent(CH_2Cl_2,ether,THF, dioxane,toluene) together with tetrabutylammoniumhydrogensulfate(TBAH) proved to be the system of choice. This general acylation principle was first tested on the acetylation of simple phenols(β-naphthol, 2,5-dichlorophenol,mesitol),anilines(aniline,p-methoxyaniline) and diethyl malonate. All these compounds were easily acetylated within a short time at room temp. or below. Even without catalyst the reaction takes place. Diethyl malonate was doubly acetylated because the introduction of the first acetyl-group provides a highly enolisable keto-function which immediately reacts with further acetyl chloride to form the enolacetate of diethyl-acetomalonate(6)[1]. Nevertheless these reactions would not convince an organic chemist to perform his acetylations under PTC-conditions. Therefore the effectiveness of this method had to be demonstrated on the acylation of the highly hindered phenol 2,6-di-tert.-butyl-p-cresol(1,2). Reactions with acetyl- and propionyl chloride were complete within two hours at room temp. with 72% and 76% yields respectively(distilled products).

Although we did not succeed in selectively acetylating the phenolic-OH in p-hydroxy-benzyl alcohol this method does nonetheless exert a certain selectivity in the acylation of phenolic versus aliphatic OH-groups. Thus β-estradiol could be acylated solely at 3-OH. Especially with lower aliphatic carbon acids this has been a tedious task so far, either by reduction of the corresponding estroneacylate[5] or by reaction of estradiol with 3-acyl-1,5,5-trimethylhydantoin[6].

3-Monoacetylation of β-estradiol:

To a well stirred mixture of estradiol(10 mmoles),dioxane(25 ml),TBAH(12 mg) and powdered NaOH(1 g) a solution of acetyl chloride(11-12 mmoles) in dioxane(10 ml) was added dropwise over 30 min. at room temp. The mixture was filtered,washed with dioxane,evaporated and dried. Average yield from four runs 90%,average purity determined by GLC 97%,M.p.138°.

No	Product	Temp.	Time min.	M.p.or b.p./torr	Yield(%)
1		r.t.	120	156-158°/13 torr	72
2		r.t.	120	122-132°/3 torr	76
3		r.t.	30	138°	90
4		r.t.	30	182-183°	94
5		r.t.	30	98-99°	89
6		r.t.	120	148-150°/15 torr	64

All products gave satisfactory elemental analyses and their structures were identified by comparison with authentic samples and ^{3}H-NMR,IR and UV-spectrometry.

The simplicity of this reaction could provide the organic chemist with a potentially attractive alternative to common acylation procedures.

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