

AN IMPROVED PROCEDURE FOR THE ACYLATION OF PHENOLS USING BORON TRIFLUORIDE-ETHERATE

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PHLOROACETOPHENONE and 2,4-dihydroxyphenyl 4-methoxybenzyl ketone are being prepared by the time-consuming Hoesch condensation of phloroglucinol with acetonitrile¹ and resorcinol with 4-methoxyphenyl acetonitrile² respectively. Nencki's method of acetylation of phenols³ with carboxylic acids in the presence of freshly fused zinc chloride does not work in the above cases. An alternative cumbersome procedure for acylation/acetylation of phenols, quinones and steroids with carboxylic acids or acetic anhydride saturated with boron trifluoride was reported⁴⁻⁷. However, the scope of this procedure to provide a general method for the preparation of phenolic ketones has not been studied⁸.

We have now carried out a detailed study on acylation of phenols using acid anhydrides in the presence of boron trifluoride-etherate and the results are presented below.

Phloroglucinol, when treated with acetic anhydride and boron trifluoride-etherate at 30° for 1 h, affords phloroacetophenone. Similar reaction of resorcinol with 4-methoxyphenyl acetic anhydride at 70–80° for 3.5 h gives 2,4-dihydroxyphenyl 4-methoxybenzyl ketone. 2,5-Dihydroxyacetophenone, β -resacetophenone, 2,3,4-trihydroxyacetophenone, 2,4-dihydroxyphenyl benzyl ketone, 2,3,4-trihydroxyphenyl benzyl ketone and 2,4-dihydro-

xybenzophenone have also been prepared by this procedure (table 1) which provides a better alternative to the use of messy freshly fused zinc chloride⁹⁻¹⁴.

The behaviour of phloroglucinol is noteworthy. While it readily affords phloroacetophenone, its reaction with benzoic anhydride, phenylacetic anhydride or its 4-methoxy derivative at various temperatures leads to the formation of complex mixtures. However, in Hoesch condensation with phenyl acetonitriles, phloroglucinol has been found to afford better yields (table 2) of the desired phenyl benzyl ketones when boron trifluoride-etherate is substituted for freshly fused zinc chloride. Hoesch condensation between resorcinol and phenyl acetonitriles in the presence of boron trifluoride-etherate does not show any improvement in yields over fused zinc chloride method; however the use of boron trifluoride-etherate is a lot more convenient.





The reaction between individual phenol and acid anhydride is sensitive to changes in temperature. Best yield of the desired product has been obtained at the temperature recorded (see table 1). The above acylation has also been found to work well in milligram quantities proving the efficiency of the method for getting labelled acetophenones for biosynthetic work.

General procedure

Acetophenones (2a–d)

Phenol (18 mmol) was magnetically stirred with acetic anhydride (22 mmol) and boron trifluoride-etherate (8.4 mmol) at the temperature and for the duration given in table 1. Ice (100 g) was added and the mixture was magnetically stirred till a solid

Table 1 Acetophenones 2,4-dihydroxy and 2,3,4-trihydroxyphenyl benzyl ketones and 2,4-dihydroxybenzophenone

2	X ¹	X ²	X ³	X ⁴	Y	Reaction		Yield
						Time [h]	Temp. [°C]	
a	H	OH	H	OH	CH ₃	1	30°	63
b	OH	OH	H	H	CH ₃	2	130°	60
c	H	OH	H	H	CH ₃	2	100°	58
d	H	H	OH	H	CH ₃	1	130–135°	45
e	H	OH	H	H	CH ₂ - 	2.5	70–75°	48
f	OH	OH	H	H	CH ₂ - 	2.5	75–80°	26
g	H	OH	H	H	CH ₂ - 	3.5	75°	67
h	H	OH	H	H		5.5	90°	31

m.p.s were in agreement with the literature values^{1,2,9-14}.

Table 2 2,4,6-Trihydroxyphenyl benzyl ketones

4	R ¹	R ²	R ³	Yield using [%]	
				ZnCl ₂ *	BF ₃ -(C ₂ H ₅) ₂ O
a	H	H	H	39	50
b	OCH ₃	H	H	42	45
c	H	H	OCH ₃	55	82
d	H	OCH ₃	OCH ₃	38	59

*Yields not available in literature^{15,16} 4d. m.p. 182–184°; calc. C 63.15, H 5.26 found C 62.90, H 5.30.

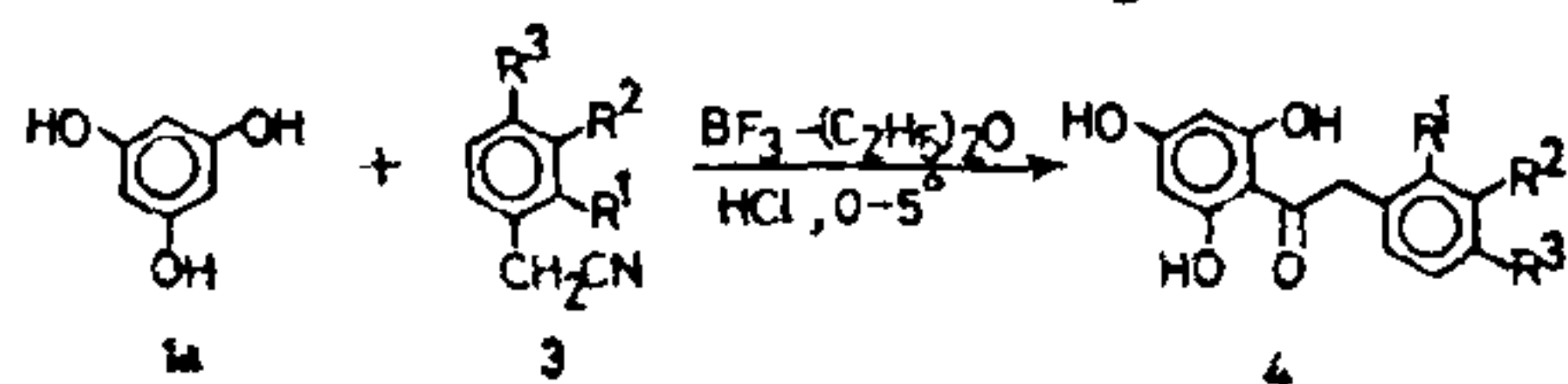
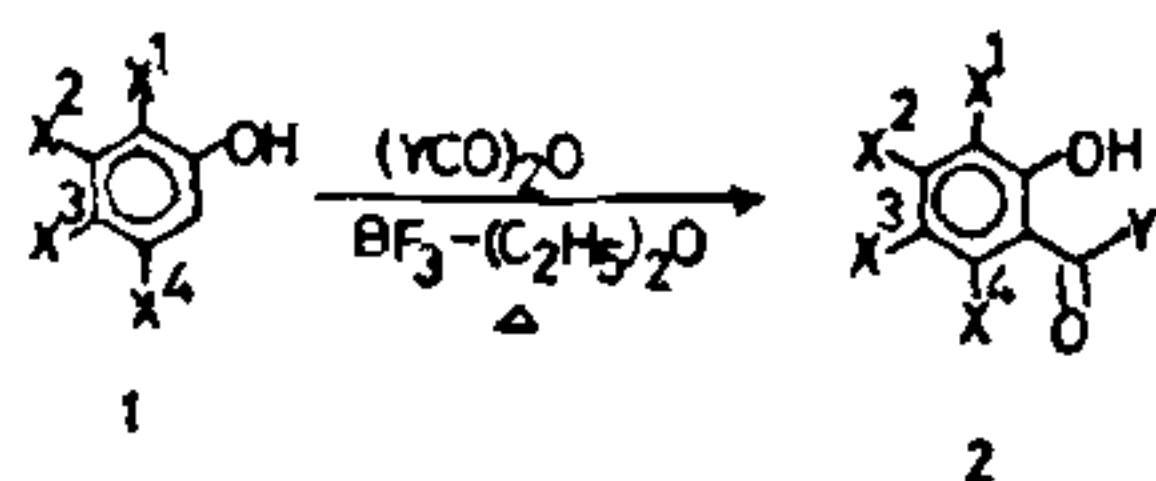
resulted. The precipitated product on recrystallization from appropriate solvent (table 1) afforded the corresponding acetophenones.

Phenyl benzyl ketones (2e-g) and benzophenone (2h)

A mixture of phenol (18 mmol), phenylacetic anhydride or benzoic anhydride (18 mmol) and boron trifluoride-etherate (40 mmol) was magnetically stirred at the temperature and for the duration given in table 1. The reaction mixture was treated with ice (100 g) and left in refrigerator for 15 h. Clear liquid was decanted and the pasty mass on mercuration with 8% aqueous sodium bicarbonate gave a solid which on recrystallization from appropriate solvent (table 1) gave the corresponding ketone.

2,4,6-Trihydroxyphenyl benzyl ketones (4a-d)

Dry hydrogen chloride was bubbled through a mixture of phloroglucinol (40 mmol), appropriate phenyl acetonitrile (34 mmol) in dry ether (100 ml) containing boron trifluoride-etherate (5 mmol) at 0–5° for 6 h. After 18 h at room temperature, the precipitated ketimine hydrochloride was washed with dry ether (2 × 20 ml) and heated with water (50 ml) at 100° for 2 h. The solid that separated on cooling after recrystallization from appropriate solvent yielded the corresponding phenyl benzyl ketones (table 2).



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