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Facile 1,2-Aryl Migration of 2-Halomethyl-2-(4′-Hydroxyphenyl) Ketals: A Novel Single Step Synthesis of 4-Hydroxyphenylacetic Acid and Its Derivatives

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FACILE 1,2-ARYL MIGRATION OF 2-HALOMETHYL-2-(4'-HYDROXY-PHENYL) KETALS : A NOVEL SINGLE STEP SYNTHESIS OF 4-HYDROXYPHENYLACETIC ACID & ITS DERIVATIVES.

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Abstract : 1,2-Aryl migration of 1-halomethyl-2-(4-hydroxyphenyl) ketals, obtained from 2-bromomethyl 4-hydroxyacetophenone, under mild basic conditions have been shown to give 4-hydroxyphenylacetic acid or its derivatives which are key intermediates in the preparation of Atenolol, a well known cardiac β-blocker.

Introduction :

4-Hydroxyphenylacetic acid (4-HPA; 1) and the corresponding amide (2) are valuable precursors for the manufacture of various molecules of medicinal value and in particular Atenolol (3) a well known β-blocker.[1]

Numerous synthesis of 1 and 2 have been reported[2-5] and the commercially preferred routes have been based on 4-hydroxymandelic acid (prepared by condensation of glyoxal with phenol). The latter through various trans-formations

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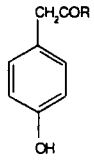
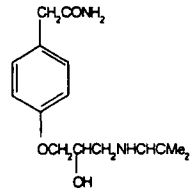


1 R = OH
2 R = NH_2

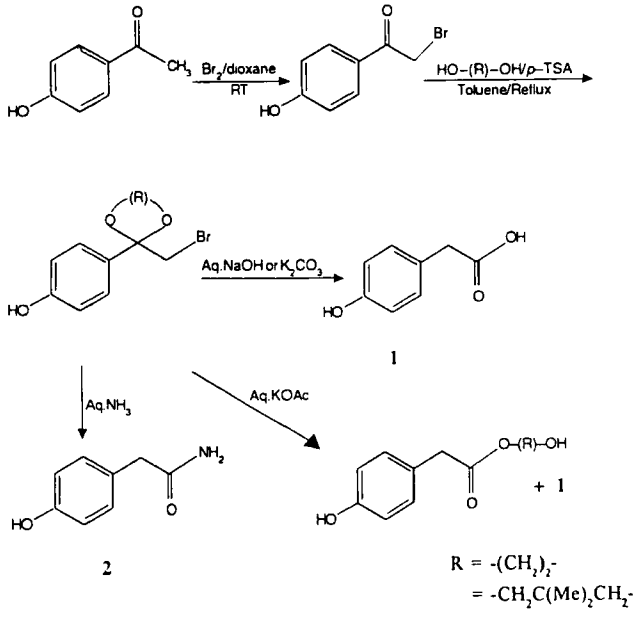


Atenolol (3)

is converted to the amide[6-12] (2). Many of these methods suffer from drawbacks such as poor material efficiency, use of expensive reagents, catalysts and in addition hazardous chemicals.

In order to circumvent these drawbacks, we have now developed an efficient and practical route for the synthesis of title compounds. Our strategy involves the use of known 1,2-aryl transposition[13] of halo ketals as a key step. The reactions generally take 0.5 to 1.5 hrs for completion yielding title compounds in high yields. Further the whole reaction sequence can be carried out in one pot without isolation of intermediates (Scheme I).

The required bromoketals are obtained from 2'-bromomethyl-4'-hydroxyacetophenone by reaction with ethylene glycol or substituted propane diols in the presence of p-TSA. Although, acidic reagents such as silver tetrafluroborate, thallium nitrate, etc.[14] have been used for the said transformation we have found that mild basic conditions are more suitable when phenyl ring bears a hydroxyl group in the p- position. For example,



SCHEME-I

when 2-bromomethyl-2-(4'-hydroxyphenyl)-1,3-dioxolane (entry 1, table 1) was subjected to treatment of aqueous NaOH at 90°C for 1 hr, 4-hydroxyphenyl acetic acid was obtained in 84% yield. However, when the corresponding dimethyl ketal (entry 2, table 1) was treated with aqueous NaOH at 95° for 40 min. 4-hydroxyphenyl acetic acid was obtained in 90% yield. Slight decrease in yield (88%) was observed when bromine was substituted by chlorine in the ketal substrate. When aqueous NaOH was replaced by aqueous potassium acetate a mixture of 4-hydroxyphenyl acetic acid and its corresponding ethylene glycol ester was obtained (entry 6, table 1) in ~80% yield.

Interestingly treatment of bromoketal (entry 7, table 1) with aqueous ammonia at ambient temperature afforded 4-hydroxylphenyl acetamide in 82.5% yield. The formation of amide product could be explained by two steps i.e. first involving 1,2-aryl migration of bromoketal to get the corresponding ethylene glycol esters which then reacts with aqueous ammonia to give corresponding amide.

It can thus be seen that the product composition could be easily manipulated by employing appropriate conditions.

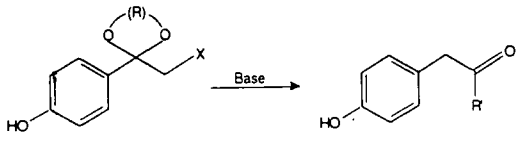
In summary, we have demonstrated a new, versatile and practical route to 4-hydroxyphenylacetic acid, amide or esters starting from α-halogenated-4-hydroxy-acetophenone as an inexpensive starting material.

Experimental :

Melting points are uncorrected and were determined with Toshniwal apparatus. Microanalysis were performed on Carlo Erba elemental analyser. IR spectra were recorded on a Perkin-Elmer 781 model. ^{1}H and ^{13}C-NMR spectra were recorded on Brucker FT-AC 80 (80 MHz) spectrometer using TMS as internal standard.

2-Bromomethyl-4'-hydroxyacetophenone (4a) :

To a stirred solution of 4-hydroxyacetophenone, (8.16 g, 60 mmol) in dioxane (14 mL) was added dropwise a solution of liq. Br_2 (3.3 mL; 61 mmol) in dioxane (55 mL) over 30 min at room temperature. The stirring was



X = Cl, Br

Table

Entry	Ketal -R-	X	Product* R′	Base used (aqueous soln.)	Reaction Temp./Time (°C)/(Hr)	Yield (%)
1	$-CH_2-CH_2-$	Br	OH	NaOH	90/1	84%
2	$-CH_2C(Me)_2-CH_2-$	Br	OH	NaOH	95/0.75	90%
3	$-CH_2C(Me)_2-CH_2-$	Cl	OH	NaOH	95/1	88%
4	$-CH_2C(Me)_2-CH_2-$	Br	OH	K_2CO_3	95/1.5	85%
5	$-CH_2-CH_2-$	Br	[OH & [OCH_2CH_2OH	KOAc	95/4	[36% [43%
6	$-CH_2C(Me)_2-CH_2-$	Br	[OH & [$OCH_2C(Me)_2CH_2OH$	KOAc	90/1	[11.7% [69.3%
7	$-CH_2C(Me)_2-CH_2-$	Br	NH_2	NH_3	RT/12	82.5%
8	$-CH_2-CH_2-$	Br	NH_2	NH_3	50/12	83.4%

continued for another 10 min and dioxane was removed under vacuum to give a buff coloured solid. The crude product was purified by column chromatography on a silica gel column using hexane-ethyl acetate (85:15)as eluent to give **4a** as white solid; yield : 10.3 g (yield based

on recovered 3, 86%); mp 130°C (lit.[15] mp 124-26°C); unreacted 3 (2.7 g) and 2,2-dibromomethyl-4'-hydroxyacetophenone **4b**, yield : 0.96 g (5.5%); mp 121-2°C. Anal. calcd. for $C_8H_6Br_2O_2$: C 32.65% H 2.04%. Found C 32.83%, H 2.11%.

IR (KBr) : = 3320, 1670, 1605, 860, 820, 680, 645 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TMS) : δ = 6.76 (s, 1H, CHBr), 6.91 (d, 2H arom, J = 8.8 Hz), 7.96 (d, 2H arom, J = 8.8 Hz). In general the purification of crude product was done by crystallisation with methanol to give **4a** of 93-95% purity.

2-Bromomethyl-2-(4'-hydroxyphenyl)-1,3-dioxolane (5):

A mixture of **4a** (4 g, 19.7 mmol; 93% pure), ethylene glycol (1.8 g, 29 mmol) and p-toluenesulphonic acid (75 mg) in toluene (50 mL) was refluxed under stirring with continuous azeotropical removal of water for 4 h. The progress of the reaction was monitored by TLC. The cooled reaction mixture was poured onto 5% aqueous K_2CO_3 solution (30 mL). The toluene layer is separated, and aqueous layer extracted with ethyl acetate (25 mL) and the combined organic layer is washed with water (2x25 mL), dried (Na_2SO_4) and concentrated to give a viscous mass which was purified by passing through a column of silica gel using hexane- ethyl acetate (9:1) as eluent to give 5 as a colourless solid, yield : 4.0 g (89%); mp 127°C. Anal. calcd. for $C_{10}H_{11}BrO_3$: C 46.33%, H 4.24%. Found C 46.63%, H 4.38%.

IR (KBr) : = 3365, 1615, 1595, 1510, 1440, 1365, 1215 cm^{-1}

^{1}H-NMR ($CDCl_3$/TMS) : δ = 3.64 (S,2H, CH_2Br), 3.9 (m, 2H, OCH_2), 4.05 (m, 2H, OCH_2), 6.7 (d, 2H arom, J=8.6 Hz), 7.25 (d, 2H arom, J=8.6 Hz).

^{13}C-NMR ($CDCl_3$/TMS) : δ = 38.1, 65.7, 107.3, 115.2, 127.5, 131.7, 156.1.

For 1,2-aryl rearrangement the purification of the ketal 5 is not necessary and a crude product was used as such in the next step.

1,2-Aryl rearrangement with NaOH : 4-Hydroxyphenyl acetic acid :

2-Bromomethyl-5,5-dimethyl-2-(4-hydroxyphenyl)-1,3-dioxolane (3.6 g, 12 mmol) was added to an aqueous NaOH solution (0.96 g NaOH in 40 ml water) and heated at 90-95^{o}C for 40 min. The reaction mixture was cooled, acidified with aqueous HCl, saturated with brine and extracted with ethyl acetate (3x30 ml). The organic layer was washed with water (2x10 ml); dried (Na_2SO_4) and concentrated under reduced pressure. The residue on crystallisation from water gave 4-hydroxyphenylacetic acid. Yield 1.6 g (88%); m.p. 148-9^{o}C.

With KOAc :

A suspension of 2-bromomethyl-5, 5-dimethyl-2-(4-hydroxyphenyl) 1,3-dioxolane (1.2 g, 4 mmol) in aqueous potassium acetate (0.78 g, in 25 ml water) was heated at 90-100^{o}C for 1 hr. The reaction mixture was extracted

with ethylacetate (3x30 ml) and the organic layer was washed with water (2x10 ml), dried over Na_2SO_4 and concentrated under reduced pressure to give a viscous mass. The latter on purification using silica gel column (hexane : ethyl acetate; 4:1, as eluent) gave 2,2-dimethyl-3-hydroxypropyl (4-hydroxyphenyl acetate); yield 0.95 g, (69.3%), m.p. 131°C and 4-hydroxyphenylacetic acid yield 0.07 g (11.7%) m.p. 148-9°C (ethylacetate : MeOH, 9:1 as eluent).

With aq. ammonia : 4-Hydroxyphenylacetamide (2) :

2-Bromomethyl-2-(4-hydroxyphenyl)-1,3-dioxolane (2.5 g, 9.65 mmol) in 25% aqueous ammonia (26 ml) was kept in a closed vessel at 50°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give viscous mass which was chromatographed on silica gel column with ethylacetate : MeOH (8:2) as eluent to give 4-hydroxyphenylacetamide, yield 1.26 g, 83.4% m.p. 169-171°C.

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