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SYNTHESIS OF 6/7- HALOTETRALONES

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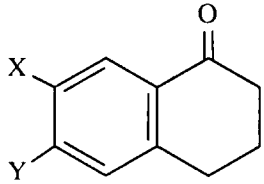
Abstract: The title compounds were prepared from halobromobenzenes via a palladium catalysed coupling followed by cyclisation.

In connection with another project we required access to a series of 6 and 7 halo-substituted tetralones (1).



X/Y = Cl, F, CF_3

1

A review of the literature revealed that a number of these compounds are unreported and others are mentioned only in passing in the patent literature[1].

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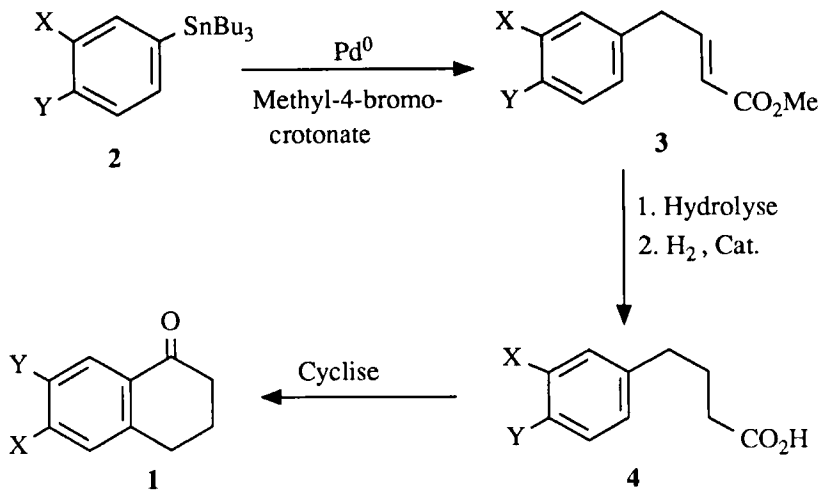
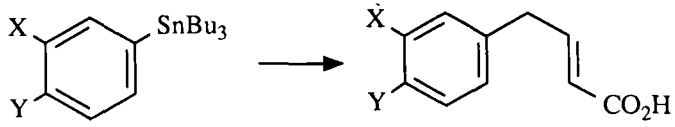


Scheme I

The usual method of synthesis of tetralones is by cyclisation of the corresponding arylbutanoic acid or derivatives[2]. A number of syntheses of arylbutanoic acids exist in the literature. However, those based on Friedel-Crafts acylation with succinic anhydride[3], followed by reduction and cyclisation give rise to 7-substituted tetralones only. Bromopropionic acid phosphonium salt has been reacted[4] with benzaldehydes to give arylbutenoic acids which were subsequently transformed into tetralones; however, the yields in this reaction are reported as variable.

We therefore devised a route based on the palladium catalysed coupling of aryltributylstannanes with methyl-4-bromocrotonate[5] to give 4-arylbutenoates. These compounds may then be transformed to the required tetralones under literature conditions[3,4] (scheme I).

Table I

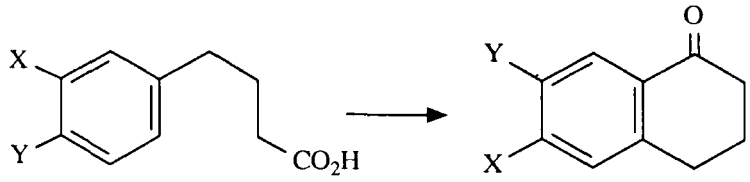


X	Y	Yield* (%w.r.t $ArSnBu_3$)
H	Cl	74
H	F	72
Cl	H	86
F	H	91
F	F	71
Cl	Cl	73
H	CF_3	74

* all yields are quoted as mixtures of but-2-enoic and but-3-enoic acids

Aryltributylstannanes (2) are available in nearly quantitative yield by Bu_3SnCl trapping of magnesium or lithium aryls. Coupling with methyl 4-bromocrotonate took place in the presence of Pd^0 in refluxing tetrahydrofuran. The hydrolysis of the resulting esters (3) was achieved in a one pot procedure by the addition of LiOH (2.5eq) and a small amount of water and continuing the reflux. Extraction into aqueous base of the resulting lithium carboxylate, acidification and re-extraction into organic gave the required arylbutenoic acids (table I).^{1}H N.M.R. showed the products to be mixtures of arylbut-2-enoic and arylbut-3-enoic acids. Hydrogenation of the mixtures over 10% Pd-C gave the arylbutanoic acids(4).

Table II



X	Y	Yield (%)
H	Cl	80
H	F	61
Cl	H	45
F	H	70
F	F	39
Cl	Cl	36
H	CF_3	see text

Cyclisation with polyphosphoric acid (PPA) under the literature conditions[3] gave the required tetralones (table II), except for the trifluoromethyl product which failed to give any tetralone with PPA or polyphosphate ester. Formation of 4(4'-trifluoromethylphenyl)butanoyl chloride followed by reaction with $AlCl_3$ in 1,2-dichloroethane gave 7-trichloromethyl-1-tetralone in 33% yield.

Experimental:

Aryltributylstannanes were prepared from the commercially available bromohalobenzenes by Bu_3SnCl trapping of the magnesium or lithium aryls. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.

Coupling of Methyl 4-bromocrotonate & Aryltributylstannane

General Procedure:- Bis(triphenylphosphine)palladium(II) chloride (Aldrich) (300mg) was suspended in tetrahydrofuran(100ml) under N_2. DIBAL-H (1M in toluene)(Aldrich)(1ml) was added by syringe and the mixture was stirred for 5 minutes at 25^0C. A solution of methyl 4-bromocrotonate (Aldrich)(10.5g, 60mmol) and the aryltributylstannane(60mmol) in tetrahydrofuran(50ml) was added. The reaction mixture was heated under reflux for 15 hours under N_2. The solvent and unreacted crotonate was removed under reduced pressure and the residue dissolved in tetrahydrofuran(90ml). Water(10ml) and lithium hydroxide hydrate(Aldrich)(5g) was added and the reaction mixture was heated under reflux for 6 hours. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between ether and 2N sodium hydroxide solution. The organic phase was washed with 2N sodium hydroxide solution and the combined aqueous phases were washed with ether and then acidified with 5N hydrochloric acid. The aqueous phase was extracted with dichloromethane(x3). The combined organic phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude arylbutenoic acid.

Hydrogenation of Arylbutenoic Acid

General Procedure:- Arylbutenoic acid was dissolved in ethanol(100ml) to which was added 10% Pd on charcoal(150mg). The mixture was hydrogenated at 50 p.s.i. for 12 hours. The mixture was filtered (Celite) and the solvent removed at reduced pressure to give arylbutanoic acid.

Cyclisation of Arylbutanoic Acid

Arylbutanoic acid was cyclised with polyphosphoric acid by the procedure described in ref. 3.

Cyclisation of 4(4'-Trifluoromethylphenyl)butanoic Acid

4(4'-Trifluoromethylphenyl)butanoic acid was transformed to its acid chloride and cyclised by the procedure described in ref. 4, the only alteration being the use of 1,2-dichloroethane as solvent.

6-Chloro-1-tetralone B.p. 150°C / 0.7mm

M^+ found 180.0352 calculated 180.0342

^1H N.M.R. 2.12 2H(m), 2.63 2H(t), 2.93 2H(t), 7.23 1H(d), 7.24 1H(dd), 7.94 1H(d).

I.R. CO 1688 cm^{-1}.

7-Chloro-1-tetralone Mpt. 79-81°C

M^+ found 180.0342 calculated 180.0342

^1H N.M.R. 2.14 2H(m), 2.65 2H(t), 2.93 2H(t), 7.21 1H(d), 7.42 1H(dd), 7.99 1H(d).

I.R. CO 1675 cm^{-1}.

6,7-Dichloro-1-tetralone Mpt. 77-79°C

M^+ found 213.9932 calculated 213.9952

^1H N.M.R. 2.14 2H(m), 2.65 2H(t), 2.92 2H(t), 7.38 1H(s), 8.08 1H(s).

I.R. CO 1681 cm^{-1}.

6-Fluoro-1-tetralone B.p. 75°C / 0.6mm (lit[2a] 105°C / 3mm)

M^+ found 164.0629 calculated 164.0637

^1H N.M.R. 2.13 2H(m), 2.63 2H(t), 2..95 2H(t), 6.91 1H(d), 6.97 1H(dd), 8.04 1H(d).

I.R. CO 1679 cm^{-1}.

7-Fluoro-1-tetralone Mpt. 48-49°C

M^+ found 164.0647 calculated 164.0637

^{1}H N.M.R. 2.15 2H(m), 2.65 2H(t), 2.94 2H(t), 7.17 1H(dd), 7.23 1H(d), 7.69 1H(d).

I.R. CO 1679 cm^{-1}

6,7-Difluoro-1-tetralone Mpt. 26-28^{0}C

M^+ found 182.0557 calculated 182.0543

^{1}H N.M.R. 2.15 2H(m), 2.64 2H(t), 2.93 (t), 7.06 1H(dd), 7.83 1H(dd).

I.R. CO 1690 cm^{-1}.

7-Trichloromethyl-1-tetralone Mpt. 42-44^{0}C

M.S. (DCI) 280($M+NH_4$), 263(M+H), 227(M-Cl).

^{1}H N.M.R. 2.17 2H(m), 2.70 2H(t), 3.01 2H(t), 7.37 1H(d), 8.02 1H(dd), 8.58 1H(d).

^{13}C N.M.R. 22.8, 29.4, 38.9, 96.9, 124.6, 129.4, 130.1, 132.1, 143.1, 146.6, 197.6.

I.R. CO 1686 cm^{-1}

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