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SYNTHESIS OF LONG CHAIN ω-ARALKYLBROMIDES

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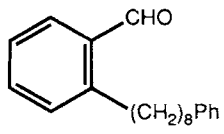
Abstract - 1-Iodo-4-acetoxybutane is a useful 4 carbon synthon which reacts selectively with Grignards under copper catalysis. The immediate products are converted to bromides.

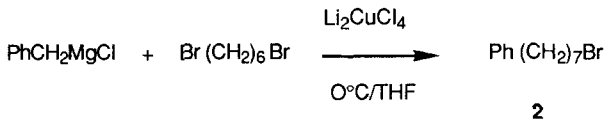
2-(8-Phenyloctyl)benzaldehyde **1** is a strategic intermediate in the synthesis of leukotriene antagonists.[1]



1

Increasing demand for **1** for the drug development process meant that kilogram quantities were required by a direct, high yielding and efficient process. Such a process was discovered[2] whereby o-toluic acid was alkylated with 1-bromo-7-phenylheptane **2**. Compound **2** was easily obtained in one step by the reaction of benzylmagnesium chloride and dibromohexane using catalytic[3] Li_2CuCl_4 (Scheme 1).

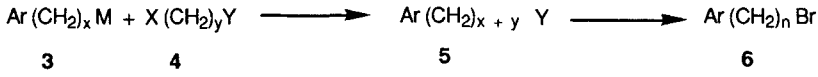
Scheme 1



Although kilogram quantities of **2** were available by this process, the synthesis had several disadvantages. The 50% yield was moderate, a consequence of the statistical nature of the reaction, but more significantly fractional distillation was required to separate **2** from the excess of dibromohexane used to minimise bis coupling. On large scale this was not only costly and time consuming but the recovery of **2** from material available was only 65 - 70%, effectively reducing the practical yield to 33-35%. As a result of this we looked for a more efficient synthesis of **2** and now wish to report a synthesis from readily available materials which avoids fractional distillation.

Our approach was to use a suitably differentiated bifunctional alkane which would initially be reacted with an aralkylorganometallic at one end and converted to a bromide at the other end. [Scheme 2 (n = 4 to 9)].

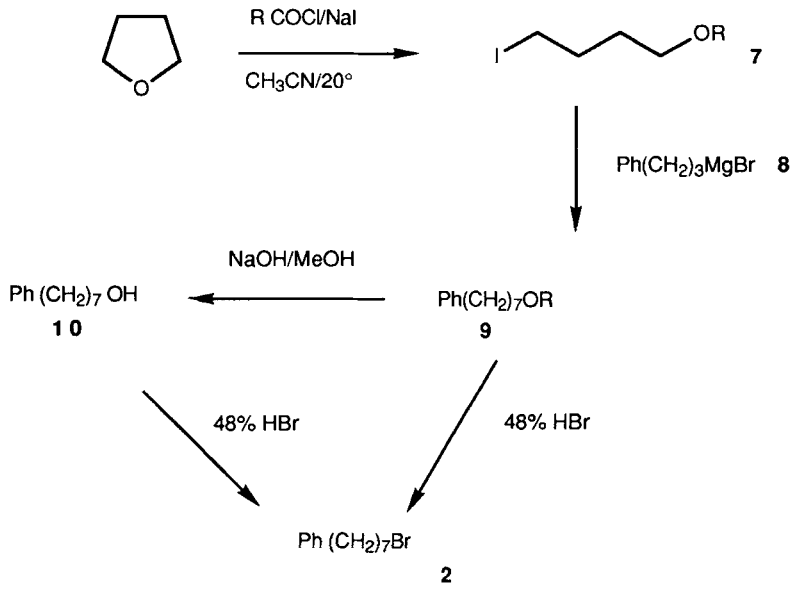
Scheme 2



Of particular interest to us was the availability of potential precursors **3** and **4** and the challenge of controlling the chemistry such that **5** was efficiently synthesised as 7-phenylheptan-1-ol, the conversion of which to **2** has been reported[4].

In looking for suitable precursors **4** we were attracted by 1-iodo-4-acetoxybutane. This was readily available[5] as the product from sodium iodide/acetyl chloride cleavage of THF. This is a general reaction and other esters (e.g. pivaloate and benzoate) are produced using the respective acid chlorides. Selective reaction of 7-phenyl-1-propyl Grignard at the halogen would provide 1-acetoxy-7-phenylheptane, a suitable precursor of **2**. Though initially such selectivity was thought unlikely we were encouraged by a report[6] that 1-iodo-4-acetoxybutane **7** reacted selectively under Cu I catalysis with the Grignard derived from 2-(2-bromoethyl)-1,3-dioxane in the desired manner.

Scheme 3



In the event, reaction of phenylpropylmagnesium bromide **8** (Scheme 3) with **7** as the acetate or pivaloate in the presence of catalytic Li_2CuCl_4 gave the phenylheptyl esters **9** in 59 and 57% yields respectively. Base hydrolysis (NaOH/MeOH) of **9**

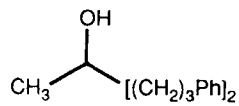
gave 7-phenylheptan-1-ol **10** from which **2** was obtained by treatment with hydrobromic acid. More conveniently **2** was obtained directly from the acetate (**9**, R = CH_3CO) by refluxing with hydrobromic acid, although this was unsuccessful with the pivaloate ester (**9**, R = Bu^tCO). These results established the viability of the reaction sequence and we therefore investigated the individual steps in more detail for acetates.

We found that cleavage of THF to **7**(R=CH_3CO) occurred in the absence of acetonitrile at 25 - 40°/3hr. This substantially simplified the literature procedure since, by simply filtering off the sodium chloride, ester **7** could be used as a solution in the cyclic ether (98% solution yield). Alternatively **7** can be separated and isolated in 87% yield by distillation.

Addition of Grignard **8** to iodoacetate (**7**, R=CH_3CO) in THF/Li_2CuCl_4 (0.05 equiv.) at 20°C gave the desired ester (**9**, R = CH_3CO) in 59% yield, along with 6.7% of 1,8-octanediol diacetate **11**. We presumed that **11** was formed by a Grignard exchange with **7** and reaction with further iodoester (**7**, R=CH_3CO). The presence of diacetate **11** was unacceptable because it converted through to 1,8-dibromooctane whose removal, again, required efficient fractional distillation.

Reversing the order of addition i.e. adding acetate (**7**, R=CH_3CO) to Grignard **8** eliminated formation of diacetate **11** but gave considerable quantities of the tertiary alcohol **12**.

11



12

Thus, with excess Grignard attack at the ester carbonyl was competitive and selectivity was lost. Selectivity was also lost, and only alcohol **12** was formed when the reaction was run in the absence of catalyst. However by adding Grignard **8** (1.2 equiv) and iodoacetate (**7**, R = CH_3CO), simultaneously to the catalyst in THF, the level of diacetate **11** was reduced to 1 - 2% and the yield of (**9**, R = CH_3CO) raised to 65%. This dual addition procedure has been adopted as the preferred mode of operation.

Direct conversion of acetate (**9**, R = CH_3CO) to bromide **2** was initially thought to proceed by hydrolysis to alcohol **10** followed by bromide formation. However, analysis showed that **10** was not detected; this meant that either **10** was formed and converted very quickly to the bromide or direct displacement of acetoxy by bromide was occuring. The evidence suggests that the latter was occuring because in comparative experiments conversion of **10** to **2** required 20 h, whereas acetate **9** was converted to bromide **2** in only 6 h.

We have demonstrated an overall 3 step process to 1-bromo-7-phenylheptane **2** from readily available materials. THF is cleaved by NaI/AcCl to give (**7**, R=CH_3CO) which, without isolation, is reacted with Grignard **8** to give 1-acetoxy-7-phenylheptane in 63% overall yield. This may be isolated and purified or alternatively converted directly to the bromide. Purification of the bromide is facile by distillation and impurities are present in relatively low levels. This process is more cost effective than that showed in Scheme 1.

The generality of the process for the preparation of other aralkyl bromides is demonstrated by the examples in the table. The chemistry in Scheme 2 is of even greater generality than the examples might indicate, since Grignard formation from **6** and repetition of the sequence allows further access to higher homologues.

Grignard	Iodoacetate[1]	Bromide	Yield (%)[2]
Phenyl	Butyl	4-phenyl-1-butyl	78
Phenyl	Pentyl	5-phenyl-1-pentyl	76
Phenethyl	Butyl	6-phenyl-1-hexyl	52
Phenylpropyl	Pentyl	8-phenyl-1-octyl	46

(1) 1-iodo-5-acetoxypentane is prepared by cleavage of tetrahydropyran under the same conditions as THF.

(2) Yield from the iodoacetate over 2 steps.

Experimental

Reagents were used as received from suppliers. Reactions involving Grignards were carried out under an atmosphere of nitrogen. GC analyses were carried out using a J&W DB-5, liquid phase, 15 m x 0.55 mm column.

1-Iodo-4-acetoxybutane : (7,R = CH_3CO)

Acetyl chloride (39.8 g - 0.05 mole) was added over 40 minutes with cooling at 30°C to a stirred mixture of sodium iodide (90 g - 0.6 mole) and THF (92 ml). The mixture was stirred at 30°C for a further 3 h. It was cooled to 20°C, the precipitated sodium chloride filtered off and washed with THF (50 ml). The solvent was removed under vacuum and the residue distilled (88°C, 4 mbar) to give the product (105.3 g - 87.8% yield).

^1H NMR ($CDCl_3$) 4.15-4.05 (t, 2H), 3.25 - 32 (t, 2H), 2.06 (s, 3H); 1.95 - 1.85 (m, 2H); 1.80 - 1.70 (m, 2H).

Note: The 1-iodo-4-acetoxybutane may be used as a solution in THF. After filtration of the sodium chloride and THF wash the molarity of the solution is 3.64 by NMR. Solution yield was 98% as determined by analysis for iodine.

1-Iodo-5-acetoxypentane:

This was prepared by the same method as for 1-iodo-4-acetoxybutane. On a 0.5 mole scale (acetyl chloride) the product, 1-iodo-5-acetoxypentane, was again obtained by distillation (98.8 g - 77% yield).

^{1}H NMR ($CDCl_3$) 4.15 - 4.05 (t, 2H), 3.25 - 3.18 (t, 2H); 2.05 (s, 3H), 1.95 - 18 (m, 2H); 1.75 - 1.6 (m, 2H); 1.55 - 1.42 (m, 2H).

1-Acetoxy-7-phenylpropane (**9**, R = CH_3CO) (Preferred method, dual addition).

Copper (II) chloride (11.4 g, 0.085 mole) and lithium chloride (7.2 g, 0.17 moles) were dissolved in THF (1L). Methylmagnesium bromide (Aldrich, 85 ml of 3M solution, 0.25 mole) was added. Phenylpropylmagnesium bromide[7] in THF (1.2 L of 1.43 M, 1.7 moles) and iodoacetoxybutane in THF (1.05 L, 1.43 M, 1.5 moles) were added simultaneously at the same rate keeping the temperature between 5 and 10°C. The mixture was allowed to warm 25°C and after 1 h was shown to be complete by GC analysis. Saturated ammonium chloride (1 L) was added below 30°C and the separated organic phase successively washed with saturated sodium thiosulphate (0.5 L) and 10% sodium chloride solution (3 x 1 L). The solvent was removed under vacuum to leave the product as an oil ; 388 g containing 230 g (65.3% yield) of phenylheptylacetate by LC assay. This was used without purification.

Other major components by GC were phenylpropane (19%), 1, 6-diphenylhexane (4.3%), 7-phenylheptan-1-ol (5.5%) and residual iodobutylacetate (4.5%).

1-Acetoxy-7-phenyl heptane can be distilled at 108°C (0.25 mbar).

^{1}H NMR ($CDCl_3$) : 7.30 - 7.10 (m, 5H); 4.08 - 4.00 (t, 2H) ; 2.62 - 2.57 (t, 2H), 2.02 (s, 3H); 1.08 - 1.52 (m, 4H) ; 1.4 - 1.25 (m, 6H).

1-Bromo-7-phenyl heptane (2)

1-Acetoxy-7-phenylpropane (117 g, 0.51 mole : 200 g unpurified at 59.3% assay) and 48% hydrobromic acid (1.05 kg, 6.2 moles) were refluxed until reaction was complete by GC (4 to 6 h). The mixture was cooled to 20°C and 60 - 80 petrol (1 L) added. The phases were separated and the organic phase washed with water (4 x 1 L). The solvent was removed under reduced pressure to leave an oil that was fractionally distilled at 122 - 124°C (1 mbar) to give 104.8 g (80.6% yield).

^{1} H NMR ($CDCl_3$) 7.35 - 7.15 (m, 5H); 3.43 - 3.35 (t,2H); 2.65 - 2.55 (t, 2H); 1.9 - 1.75 (m, 2H), 1.70 - 1.55 (m, 2H), 1.50 - 1.25 (m, 4H)

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7. Prepared by standard methods.

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