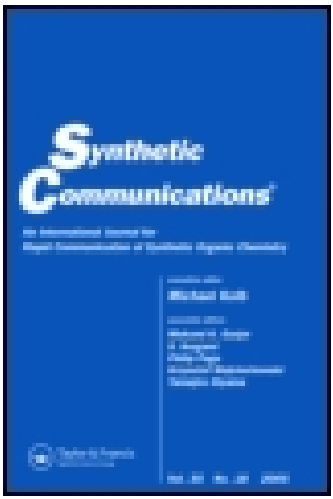

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An Organometallic Route to 2′-Hydroxy-6′-methoxy-acetophenone

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AN ORGANOMETALLIC ROUTE TO 2'-HYDROXY-6'-METHOXY-ACETOPHENONE

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ABSTRACT : 2'-Hydroxy-6'-methoxyacetophenone was obtained in 66 % yield from 3-methoxyphenol. In the key step, 3-methoxyphenol protected by means of ethylvinyl ether was selectively metallated at the 2-position with butyllithium. Addition of $ZnCl_2$ to the aryllithium gave the corresponding organozinc compound, which readily reacted on acetyl chloride under palladium catalysis.

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The procedure used previously for the preparation of 2'-hydroxy-6'-methoxy-acetophenone comprises 4 steps from commercially available resorcinol to 2', 6'-dihydroxy-acetophenone. The overall yield was 31-52%. [1,2] One step involving the Fries rearrangement, usually gives the isomeric acetyl derivative-4-methyl-6-acetyl-7-hydroxy coumarin as a coproduct[3].

2'-Hydroxy-6'-methoxyacetophenone was synthesized by the action of dimethylsulfate in benzene on 2', 6'-dihydroxyacetophenone[4]. Thus the overall yield of 2'-hydroxy-6'-methoxyacetophenone from resorcinol was less than 44%. The versatility of 2'-hydroxy-6'-methoxyacetophenone as intermediate was demonstrated by its transformation into different heterocyclic systems with extended biological activities, for example : flavones,[5] coumarins,[6] chalcones,[7] phenylethylamines.[8]

Coupling reaction of acyl halides and organometallic compounds is one of the most fundamental methods for ketone synthesis. The major side reaction is the addition of the organometallic compounds to the produced ketone.[9] Side reactions have been excluded by employing various organometallic reagents such as organomagnesium,[10] - copper,[11] manganese,[12] - zinc,[13-14] and others under well defined conditions.

In this paper, we report a simple method for the synthesis of 2'-hydroxy-6'-methoxyacetophenone from 3-methoxyphenol. Protected 3-methoxyphenol **1** is selectively lithiated at the 2 position by means of butyllithium. Subsequent, addition of $ZnCl_2$ produces the corresponding arylzinc **2**. The reaction between the organozinc **2** and acetylchloride, catalyzed by palladium complexes, leads to the ketone **3** under mild conditions. After deprotection of the phenol function the ketone **4** is obtained in good yields 56-66%. We have found that the organozinc

compound reacts readily with acetyl chloride in THF at 0°C in the presence of a catalyst in 2 mol % generated from $Cl_2Pd(PPh_3)_2$ and i-Bu_2AlH. The product yield is 66 %.

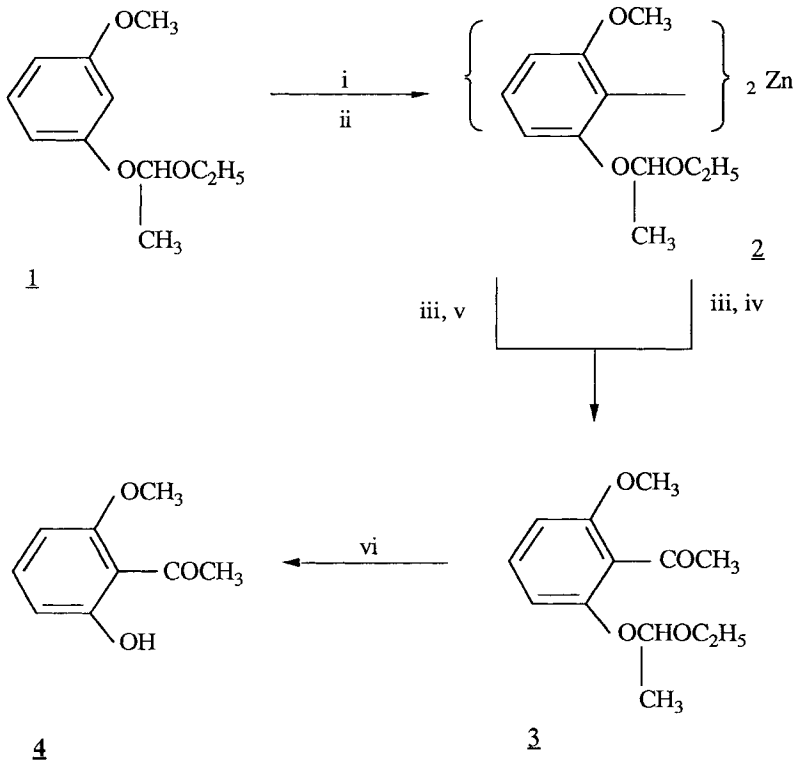
The acylation in the presence of benzylchlorobis(triphenylphosphine) palladium gives 2'-hydroxy-6'-methoxyacetophenone with a yield of 56 %. Tetrakis(triphenylphosphine)-palladium is less effective and gives the corresponding ketone a 15 % yield. Under the same conditions, the uncatalyzed reaction gives only 5 % yield of product.

EXPERIMENTAL

Melting points were determined on an Kofler melting point apparatus and are uncorrected. Elemental analysis were performed by Microanalytical Service (Gif-sur-Yvette). The IR spectra were recorded on a Perkin-Elmer 1310 Infrared spectrophotometer in $CHCl_3$. The ^1H-NMR spectra were recorded on a Bruker WM-250 spectrometer in $CDCl_3$ with TMS as internal reference. Kieselgel 60 (particle size 0.04-0.063 mm) of Merck was used for column chromatography using solvent system chloroform/hexane (8:2, v/v). Percent yields of 2'-hydroxy-6'-methoxyacetophenone were determined by capillary GLC analysis (Carbo Erba Strumentazione 4130) : 0V1, 25 m, 105°C, carrier H_2 using benzoic acid butylester as internal standard. THF was dried by distillation from $LiAlH_4$ under an atmosphere of dry argon and all reactions were routinely carried out under dry nitrogen or argon atmospheres.

The solutions of n-BuLi (1.6 M in hexane), $ZnCl_2$ (1.0 M in ether) and i-Bu_2AlH (1.0M in hexane) were commercially available (Aldrich). Benzylchlorobis(triphenyl-phosphine)palladium was prepared according to the literature procedure[15] by the reaction of benzyl chloride and tetrakis(triphenyl-

phosphine)palladium (Janssen Chimica). The catalyst "in situ" was generated from $Cl_2Pd(PPh_3)_2$ (Janssen Chimica) and 2 equiv. of i-Bu_2AlH.[16] 3-Methoxylphenol was protected as the 1-ethoxyethyl ether using Cl_3CCOOH as catalyst.



Scheme

i– n-BuLi (1.2 equiv), THF, room temp., 2h ; ii– $ZnCl_2$(0.64 equiv), THF, room temp., 1h ; iii– AcCl (1.5 equiv), THF, 0°C ; iv– $Cl_2Pd(PPh)_3$ and i-Bu_2AlH- "in situ"- 2 mol%, 0°C ; v– benzylchlorobis(triphenylphosphine) palladium- 2 mol% ; vi– HCl, methanol.

2'-Hydroxy-6'-methoxyacetophenone

a) Preparation with palladium catalyst generated "in situ"

The 1.6 M solution of n-BuLi in hexanes (7.48 ml ; 12 mmol) was added dropwise at room temperature during 15 min to a solution of 3-methoxyphenol-1-ethoxyethyl ether (**1**) (1.96 g ; 10 mmol) in THF. The yellow solution was stirred for 2 h under N_2. A 1.0 M solution of $ZnCl_2$ in ether (6.4 ml ; 6.4 mmol) was added dropwise with stirring. The reaction mixture was stirred at room temperature for 1 h to ensure complete conversion to organozinc compound (**2**). The slurry containing a white precipitate was cooled to 0°C. THF (3ml), AcCl (1.07 ml ; 15 mmol), and a mixture of $Cl_2Pd(PPh_3)_2$ (0.14 g ; 0.2 mmol) and i-Bu_2AlH (0.4 ml ; 0.4 mmol) in 4 ml of toluene were added over a 15 min period. The reaction mixture was then stirred in an ice bath for 30 min and at 25°C for 1 h to ensure complete reaction. 2 M HCl (5 ml) in 3 ml MeOH was added dropwise to the stirred reaction mixture. Brine and ether was then added, the organic layer was separated off and the aqueous layer was extracted with ether. The combined organic layers were washed with water, brine and dried over $MgSO_4$ and filtered. After removing the solvent under reduced pressure 1.5 g (90 %) of crude product (**4**) was obtained. The pure product was isolated from the residue by silica gel column chromatography using chloroform/ hexane (8:2, v/v) to obtain an off-yellow crystalline solid (1.1 g, 66 %), m.p. 58-60°C.

^{1}H-NMR ($CDCl_3$), δ(ppm) : 13.28 (1H, s, OH) ; 6.38-7.35 (3H, m, ArH) ; 3.90 (3H, s, OCH_3) ; 2.68 (3H, s, $COCH_3$) ; IR : 1630 cm^{-1} (C=O), 2990 cm^{-1} (OH)

Anal. calcd. for $C_9H_{10}O_3$:	C 65.05	H 6.07	O 28.89
found	C 65.31	H 6.31	O 28.75

b) Preparation with benzylchlorobis(triphenylphosphine)palladium

The procedure above was followed except for adding benzylchlorobis (triphenylphosphine)palladium (150mg, 0.2 mmol) instead of catalyst "in situ". After work-up and column chromatography the 2'-hydroxy-6'-methoxyacetophenone was obtained (0.930g, 56%). The ^{1}H-NMR and IR spectra and elemental analysis are in agreement with its structure.

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