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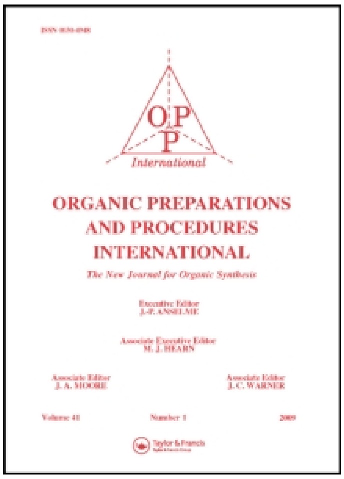

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A CONVENIENT PREPARATION OF 4-VINYLPHENYLACETIC ACID AND ITS METHYL ESTER

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A CONVENIENT PREPARATION OF 4-VINYLPHENYLACETIC ACID AND ITS METHYL ESTER

Submitted by
(03/15/94)

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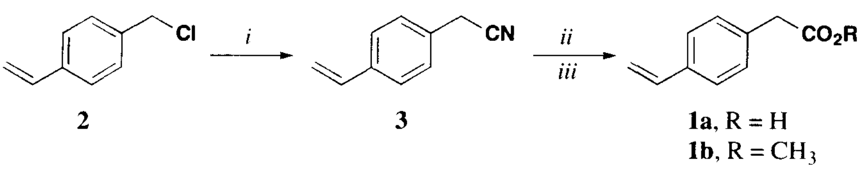
4-Vinylphenylacetic acid (**1a**) is a potential intermediate for the preparation of a variety of 1,4-disubstituted benzene compounds *via* the differential functionalization of the benzoate ester and olefin groups. The preparations of **1a** and **1b** reported in the literature suffered from several disadvantages; **1a** has been prepared most often by the Friedel-Crafts acetylation of methyl phenylacetate, followed by sodium borohydride reduction and dehydration.[1] The Friedel-Crafts reaction is not regioselective, and the intermediate ketone must be purified by low-temperature crystallization.[2] The only other synthesis of **1a** appears in the patent literature, from 1,4-diethylbenzene in an inconvenient four step process,[3] or from the corresponding nitrile **3**, the preparation of which was not given.[4] We now describe the synthesis of **1b** in three steps and 80-85% overall yield, taking advantage of commercially available, isomerically pure and and reasonably inexpensive ($80/mol) 4-vinylbenzyl chloride (**2**).



i) KCN, dicy-18-Cr-6, MeCN. *ii*) KOH, EtOH, reflux. *iii*) $KHCO_3$, Me_2SO_4, MEK, reflux

Our synthesis involves conversion of **2** to the nitrile **3** by reaction with dry potassium cyanide and dicyclohexyl-18-crown-6 in acetonitrile, followed by hydrolysis of **3** to the acid with potassium hydroxide in aqueous ethanol to afford **1a**, and finally esterification of **1a** with potassium bicarbonate and dimethyl sulfate to give **1b**.[5] The acid **1a** is purified by a simple extractive workup which also allows the crown ether to be recovered in sufficiently pure state for reuse. The ester **1b** is purified by vacuum distillation. Surprisingly, only one reference to this route exists, in which the preparation of a mixture of 3- and 4-vinylphenylacetic acid isomers from a mixture of the vinylbenzyl chlorides was reported in a Japanese patent.[6]

The efficient preparation of **3** from **2** required some optimization of reaction conditions. Reaction of **2** with potassium or sodium cyanide in DMF was attended by the formation of appreciable quantities of the isonitrile. Homogeneous or heterogeneous reaction of **2** with cyanide in the presence of hydroxylic solvents led to slower reaction and significant solvolysis of **2**.[7] The use of KCN in acetonitrile gave rapid reaction, no detectable amounts of solvolytic products or isonitrile, and allowed the destruction of cyanide residues in a water - only waste stream. It should be noted that the success of this reaction depends critically upon the particle size of the KCN, which was mechanically ground to a fine powder.[8]

The possibility of converting **2** to **1b** in one step by carbonylation with carbon monoxide in the presence of catalytic iron pentacarbonyl was also examined.[9] This route provided **1b** in one step and 41% yield but the safe removal and destruction of the metal carbonyl present in the crude product made this route unattractive for large scale work.

EXPERIMENTAL SECTION

4-Vinylbenzyl chloride was obtained from Kodak (Cat. 158 1677). GC and ^1H NMR analysis indicated this material to be ≥99% para isomer. All other reagents were purchased from J. T. Baker. All reagents were used as received. Reactions were carried out under nitrogen. Evaporations were carried out on a rotary evaporator using aspirator pressure. **CAUTION:** Both potassium cyanide and dimethyl sulfate are *highly toxic!* All operations involving potassium cyanide and dimethyl sulfate must be conducted in a good fume hood. Reaction vessels containing potassium cyanide or dimethyl sulfate should be surrounded by a secondary containment vessel large enough to contain the contents of the reaction flask should breakage occur.

4-Vinylphenylacetonitrile (3).- 4-Vinylbenzyl chloride (30.58 g, 0.20 mol) in 15 mL of CH_3CN was added to a mixture of dicyclohexyl-18-crown-6 (3.19 g, 8.5 mmol) and powdered KCN (19.5 g, 0.30

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mol) in 150 mL of CH_3CN in a 500 mL 3-neck flask fitted with a thermometer, nitrogen inlet and mechanical stirrer. The temperature of the reaction mixture rose quickly to 40° and was checked at this temperature by the brief application of a cold water bath. The reaction mixture was stirred at 25° for 16 hrs, after which time tlc analysis (silica gel; 5:1 hexane-Et_2O) showed the reaction to be complete. The CH_3CN was evaporated and the residue partitioned between water (100 mL) and Et_2O (100 mL).[10] The ethereal extract was washed with water (50 mL), brine, dried ($MgSO_4$) and concentrated to afford 34.8 g (≈ 100%) of an oily mixture of crude **3** and residual crown ether. ^1H NMR ($CDCl_3$): δ 7.40 (d, 2 H); 7.27 (d, 2 H); 6.68 (d of d, 1 H); 5.75 (d, 1 H); 5.27 (d, 1 H); 3.73 (s, 2 H). MS (NH_3 CI): *m/z* = 143 (M^+).

4-Vinylphenylacetic Acid(1a).- Crude **3** was added to a solution of 94 g (1.42 mol) of 85% KOH pellets and 0.5 g of hydroquinone (polymerization inhibitor) in 450 mL of 95% EtOH in a 1000 mL 3-neck flask fitted with a thermometer, nitrogen inlet, condenser, and magnetic stirrer. The mixture was heated at reflux for 6 hrs with a slow stream of nitrogen passing through the flask to remove NH_3 until the reaction was complete by tlc (silica gel; EtOAc). The mixture was concentrated to 200 mL and poured into 600 mL of water and extracted with Et_2O (3 x 150 mL).[11] The aqueous phase was made acidic (pH 1) with 12 M HCl and extracted with $CHCl_3$ (2 x 350 mL). The combined $CHCl_3$ extracts were washed with water and brine, dried (Na_2SO_4) and evaporated to yield 29.3 g (95%) of **1a**, mp 91-93, lit.[2] 90-91°C. ^1H NMR ($CDCl_3$): δ 7.37 (d, 2 H); 7.23 (d, 2 H); 6.68 (m, 1 H); 5.72 (d, 1 H); 5.23 (d, 1 H); 3.63 (s, 2 H). MS (NH_3 CI): *m/z* 163 (M + H^+); 180 (M + NH_4^+).

Methyl 4-Vinylphenylacetate (1b).- The acid **1a** (29.0 g, 0.179 mol) was dissolved in 450 mL of 2-butanone in a 1000 mL 3-neck flask fitted with a thermometer, condenser, and mechanical stirrer. Hydroquinone (0.5 g) and 35.8 g (0.358 mol) of powdered $KHCO_3$ was added. The mixture was heated to reflux with mechanical stirring, at which point 17.0 mL (0.179 mol) of dimethyl sulfate was added dropwise (carbon dioxide is evolved!). Heating was continued for 16 hrs, after which the reaction mixture was cooled, filtered, and the filtrate was evaporated. The oily residue was partitioned between water (400 mL) and $CHCl_3$ (400 mL). The $CHCl_3$ extract was washed with water and brine, dried ($MgSO_4$), concentrated, and distilled through a short Vigreux column to give 27.4 g (87%) of **1a**, bp. 95-100°C (1 torr), lit.[2] bp. 107°C (2 torr). Capillary column gas chromatography showed this material to be homogeneous. ^1H NMR ($CDCl_3$): δ 7.37 (d, 2 H); 7.23 (d, 2 H); 6.70 (m, 1 H); 5.72 (d, 1 H); 5.24 (d, 1 H); 3.69 (s, 3 H); 3.62 (s, 2 H). MS (EI): *m/z* 176 (M^+); 117 (M^+ - $C_2H_3O_2$). *Anal.* Calc'd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.07; H, 6.83.

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5. Iodomethane can replace dimethyl sulfate if an efficient condenser is used.

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7. The reaction of halides with aqueous solutions of alkali metal cyanides is usually slower than when "dry" conditions are used, presumably due to extensive solvation of the cyanide ion: see C. M. Starks and C. Liotta "Phase Transfer Catalysis: Principles and Techniques", Academic Press, New York, NY, 1978, pp. 93-103.

8. The KCN and $KHCO_3$ were powdered such that >90% of the material would pass through a 125 μ sieve using a Tekmar A-10 mill.

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10. The H_2O washes were added to 1500 mL of common bleach to destroy residual KCN.

11. The crown ether may be recovered from this solution by washing with brine, drying ($MgSO_4$), and evaporation.

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IMPROVED SYNTHESIS OF FLUOROMETHYL PHENYL SULFONE

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We recently reported a synthesis of fluoromethyl phenyl sulfone (**4**) using the "fluoro-Pummerer" synthesis which employs diethylaminosulfur trifluoride (DAST) as the fluoride source.[1] Compound **4** is an important starting material which we have used for the stereospecific synthesis of terminal vinyl fluorides.[2,3] In addition, this methodology has been applied to the synthesis of