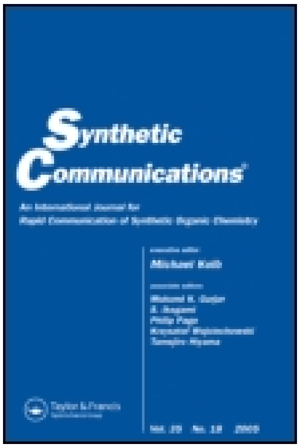

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Abstract: The preparation of the title compound has been revisited and improved. Starting from inexpensive cuminonitrile, 4-(2-hydroxy-2-methyl)-ethyl-benzylamine is obtained in a scalable two-step process with an overall yield of 55%.

Keywords: Catalysis, oxidation, phase transfer

In the course of developing a drug candidate, we required an efficient, large-scale synthesis of 4-(2-hydroxy-2-methyl)-ethyl-benzylamine (**1**, Scheme 1). The sole reported synthesis[1] of this compound, entailing a methyl Grignard addition to the corresponding ethyl ester, was impractical in our hands because of voluminous precipation of magnesium salts.

Alternatively, the known methyl Grignard additions to either methyl 4-cyanobenzoate (**2**) or 4-acetylbenzonitrile (**3**), followed by nitrile reduction, could provide an entry to the desired benzylamine.[2,3] These approaches encounter significant problems due to overaddition of methyl

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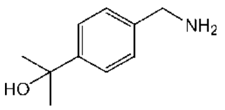


1

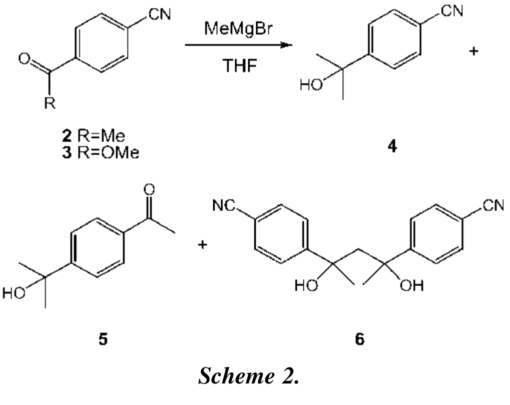
Scheme 1.

Grignard to the cyano group and enolization/self-condensation of the acetyl group, leading to the formation of the acetophenone **5** and 1,3-diol by-products[4] **6**, respectively (Scheme 2).

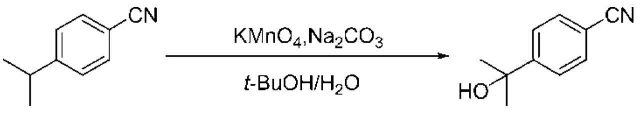
A new approach is based on the known benzylic oxidation[5] of inexpensive cuminonitrile (**7**). The original literature procedures utilize basic potassium permanganate in water to accomplish oxidation. Unfortunately, the sparse solubility of cuminonitrile in water leads to an extremely long reaction time. This issue can be addressed by use of *t*-butanol as a cosolvent, which improved the solubility of the substrate and shortened the reaction time from days to hours (Scheme 3).

However, the need for a basic medium in the oxidation causes a separate issue because the cyano group of **8** is hydrolyzed under the reaction conditions, first to the corresponding benzamide and then to the benzoic acid. This issue is easily addressed by switching from potassium hydroxide to sodium carbonate. Under these favorable conditions, the reaction proceeds smoothly at 40°C in 18 h with no observed hydrolysis of the cyano group. The simple workup entails extraction of the product into ethyl acetate. Upon displacement of ethyl acetate with heptanes, the carbinol **8** precipitates out as a crystalline solid in 67–83% yield.

Although this procedure can deliver the desired material in good yield, the reaction conditions are rather dilute with 65 L of solvent per Kg of cuminonitrile. This dilution translates into a low throughput process. In principle,



Scheme 2.



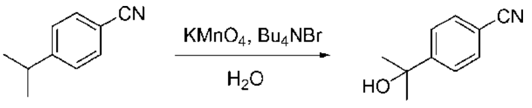
7 **8**

Scheme 3.

oxidation could be accomplished via a known benzylic oxidation procedure using tetrabutylammonium permanganate.[6] However, this phase-transfer process makes use of strongly basic reaction conditions, water, and organic solvent and is extremely dilute. It is noteworthy that tetrabutylammonium permanganate itself has been shown to be pyrophoric when isolated as a solid.[7] Therefore, a soluble permanganate salt formed in a water-exclusive phase-transfer process and utilized in situ without isolation offers a safer and potentially higher throughput alternative. A process[8] has recently been safely applied to oxidize an alcohol to the corresponding acid on production scale but with higher than desired dilution and use of expensive tetraethylammonium hydrogen sulfate as catalyst. In the present case, use of a catalytic amount of tetrabutylammonium bromide enables the desired benzylic oxidation of cuminonitrile to be performed exclusively in water, in the absence of both base and organic solvent, with high throughput. Any residual oxidant is quenched with sodium thiosulfate, and the isolation is essentially performed as described previously. Hence, application of this procedure has enabled significant reaction volume reduction from 65.0 L/Kg to 12.5 L/Kg of water (Scheme 4).

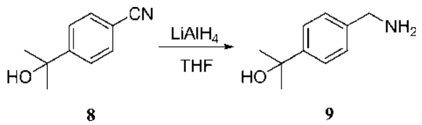
The cyano-reduction of benzonitrile **8** was fairly straightforward and was affected by lithium aluminum hydride in THF (Scheme 5). However, the resulting amine was found to be highly water soluble, and multiple extractions were required. This issue was easily resolved by applying the Fieser protocol.[9] Hence, upon quenching of the reaction with caustic, free-flowing inorganic salts were obtained, allowing for easy filtration. The tetrahydrofuran was then displaced by heptanes, and the benzylamine (**1**) precipitated out as a crystalline white solid in 82% yield.

This two-step process is extremely efficient and eliminates all the problems associated with the previously described Grignard approach. It is noteworthy that this chemistry was reproducibly scaled to multikilogram quantities.



7 **8**

Scheme 4.



Scheme 5.

EXPERIMENTAL

Melting points are uncorrected and were determined with a Thomas-Hoover unimelt apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova spectrometer operating at 400 MHz and 50 MHz respectively. The high-resolution mass spectra were recorded on a M-Scan VG analytical ZAB2SE high field mass spectrometer.

4-(2-Hydroxy-2-methyl)-ethyl-benzonitrile (8): Method A

p-Cuminonitrile (150 g, 1.03 mol) was added to a slurry of potassium permanganate (240 g, 1.52 mol) and sodium carbonate (142 g, 1.34 mol) in water (7.50 L) and *t*-butanol (2.25 L) The mixture was heated overnight at an internal temperature of 40°C. The reaction mixture was then cooled and diluted with ethyl acetate (4.50 L). The mixture was filtered to remove solids, and the filtrate was allowed to settle. The water layer was removed, and the product-rich ethyl acetate layer was washed twice with water (1.5 L) followed by saturated brine (1.5 L). The ethyl acetate layer was concentrated, and the residual ethyl acetate was displaced with heptane (4.0 L) to a final volume of 600 mL. The title compound **8** was isolated as a white crystalline solid via filtration (112.2 g, 67% yield); mp 48–51°C.

^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.75 (dd, $J = 9, 4$ Hz, 2H), 7.68 (dd, $J = 9, 4$ Hz, 2H), 5.26 (s, 1H), 1.39 (s, 6H). ^{13}C NMR (50 MHz, DMSO-d_6), δ, ppm: 156.9, 132.5, 126.3, 119.7, 109.5, 71.4, 32.1 HRMS (M + 1): calculated: 162.0919, found: 162.0908.

4-(2-Hydroxy-2-methyl)-ethyl-benzonitrile (8): Method B

p-Cuminonitrile (195 g, 1.34 mol) was added to a slurry of 2.5 L of water, tetra-*n*-butylammonium bromide (8.66 g, 26.7 mmol), and potassium permanganate (318 g, 2.00 mol) in water (2.5 L) and the resulting mixture was heated overnight at 45–50°C. The reaction mixture was cooled, sodium sulfite (10 g) was added, and it was stirred for 1 h. The reaction mixture was diluted with 2.5 L of ethyl acetate and filtered to remove solids. The water layer was removed, and the product-rich ethyl acetate layer was successively washed with of 2% aqueous sodium bisulfite (1.0 L), water (1.0 L), and saturated brine (1.5 L). The ethyl acetate layer was concentrated, and the residual ethyl acetate was displaced with heptane (4.0 L) to a final volume of 600 mL. The title compound **8** was isolated as a white solid via filtration (139 g, 64% yield). The quality of the material is consistent with those prepared in method A.

4-(2-Hydroxy-2-methyl)-ethyl-benzylamine (1)

A solution of 4-(2-hydroxy-2-methyl)-ethyl-benzonitrile (320 g, 1.99 mol) in tetrahydrofuran (900 mL) was added dropwise to a solution of lithium aluminum hydride (4.0 L, 4.0 mol, 1.0 M in tetrahydrofuran) in tetrahydrofuran (8.0 L), keeping the temperature less than 35°C. When the addition was complete, the resulting slurry was heated for 2 h at reflux. The reaction mixture was then cooled to room temperature and carefully quenched with 179 mL of water (179 mL), followed by the addition of aqueous sodium hydroxide (179 mL, 15%) and water (179 mL). The inorganic salt was removed via filtration, the product-rich THF filtrate was concentrated, and the THF was displaced with heptane (4.0 L) to a final volume of 600 mL. The title compound **1** was isolated via filtration as a white crystalline solid (270 g, 82% yield); mp 74–76°C.

^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.30 (d, $J = 8$ Hz, 2H), 7.27 (d, $J = 8$ Hz, 2H), 3.69 (s, 3H), 1.44 (s, 6H). ^{13}C NMR (50 MHz, DMSO-d_6), δ, ppm: 149.0, 141.7, 127.2, 124.9, 71.3, 32.4. HRMS (M + 1): calculated: 166.1232, found: 166.1235.

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