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An Efficient Process for the Synthesis of γ-Arylbutanals via Copper-Mediated Grignard Coupling

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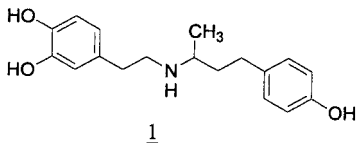
Abstract:

Copper-mediated Grignard cross-coupling of β-bromoethylene acetals with substituted benzyl halides can be combined with hydrolytic deprotection for an efficient and practical scale-up process to form γ-arylbutanals.

Introduction

Cross-coupling reactions that can be adapted to manufacturing processes are important chain-extending tools in process research. During the process development of dobutamine **1** analogues, the need arose for functionalized



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γ-arylbutanal intermediates appropriate for reductive amination with catecholamines. Both the efficiency of the process and the ease of product purification were critical for successful scale-up. In addition, reaction and isolation conditions that prevented the problematic dimerization of arylbutanals were required. There are several multistep methods reported in the literature to prepare γ-arylbutanals. Some examples involve reduction of γ-arylbutyric acid derivatives,[1] β-aroyl-propionic acids,[2] or γ-arylbutyric amides[3] and oxidation of arylbutanols,[4] which had only limited use for our scale-up requirements. As an alternative approach, we explored copper-mediated Grignard cross-couplings[5] to prepare γ-arylbutanals, since several reports in the literature have demonstrated that copper-mediated Grignard cross-coupling reactions with alkyl halides provide a mild method for chain extension.[6]

By combining a copper-catalyzed cross-coupling reaction between the Grignard reagent of 2-(2-bromoethyl)-1,3-dioxolane (or dioxane)[7] and an appropriate benzyl chloride with an in situ hydrolytic deprotection, a facile and convenient method for cleanly preparing γ-arylbutanals (Scheme 1) in high purity was achieved. The application of combining the cross-coupling and deprotection steps into a single process eliminates isolation of intermediates, minimizes purification requirements, and thereby reduces the number of overall unit operations.

Results and Discussion

The Grignard reagent of 2-(2-bromoethyl)-1,3-dioxolane *2* (Scheme 2) is prepared at 20−28 °C to avoid decomposition.[8] If the corresponding dioxane is used, the organomagnesium species can be formed in refluxing THF. During scale-up it is convenient to generate the Grignard with 1 equiv of magnesium, eliminating the need for filtration of the Grignard **2**. The coupling reaction between the Grignard **2** and 4-benzyloxybenzyl chloride is catalyzed by 0.3−0.5 mol % Li_2CuCl_4. The Kochi catalyst is prepared by dissolving 2 equiv of lithium chloride with 1 equiv of copper(II) chloride in THF. Optimal yields and fewer side products result when 4-benzyloxybenzyl chloride and the catalyst solutions are combined and then added to the cooled Grignard solution (Table 1). The order of addition played a significant role in the yields observed. The major side product of the Grignard cross-coupling is bis-4-benzyloxybenzyl ether **6**.[5,9] This by-product is minimized by using 1.4 to 1.6 equiv of Grignard reagent relative to the 4-benzyloxybenzyl chloride and by deoxygenating the THF with a nitrogen purge. The cross-coupling reaction is mildly exothermic and is easily maintained at −5 to 0 °C for 3−5 h. The reaction can then be allowed to warm to room temperature before quenching with aqueous ammonium chloride. Any undesired ether side product **6** is conveniently removed by filtration after a simple extractive workup with ethyl acetate. The

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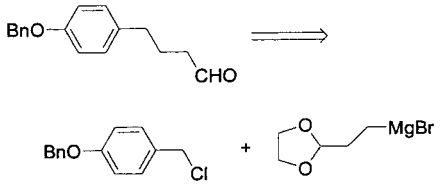
Scheme 1



Scheme 2

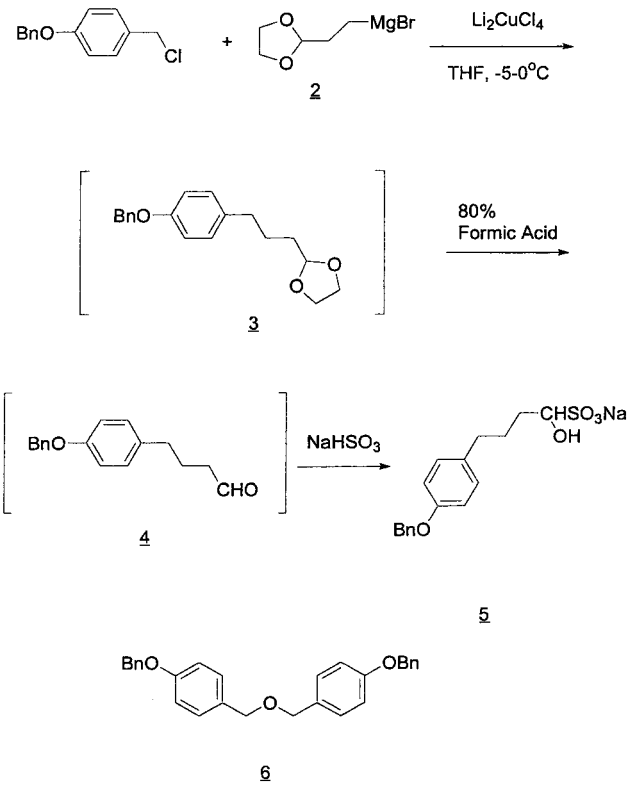


Table 1. **Effect of order of addition on copper-mediated Grignard cross-coupling**

mode of addition[a]	mg (mmol)	acetal (mmol)	benzyl chloride (mmol)	yield of isolated acetal **3**
1	24	25	23	70%
2	27	26	22	80%
3	30	28	22	86%
4	12	12	18	10%

[a] Catalyst 0.3−0.5 Mol % Li_2CuCl_4.

Order of Addition:

1= Catalyst added to solution of Grignard and benzyl halide

2= Benzyl halide solution added to mixture of Grignard and catalyst[5]

3= Solution of benzyl halide and catalyst added to Grignard

4= Benzyl halide added to solution of Grignard with catalyst

product **3** solution can be taken on directly without isolation or further purification.

The coupled product **3** is then deprotected by acid hydrolysis. While a number of acidic conditions were examined, process consistency was achieved using 80% formic acid.[10] By adding the aqueous formic acid solution directly to the crude dioxolane product **3** solution, a heterogeneous hydrolysis occurs where the dioxolane is deprotected at room temperature within 1 h (Table 2). Longer times and higher temperatures are required for the dioxane acetal. Neutralization and a simple extractive workup gives the aldehyde **4**. For campaigning convenience the product can be stored as the bisulfite adduct **5**. This is generated in situ by the addition of sodium bisulfite in isopropyl alcohol, and the resulting crystalline bisulfite adduct is collected by filtration. The overall yield for the combined two-step cross-coupling and deprotection using 2-(2-bromoethyl)-1,3-dioxolane is 53−62%. The more difficult to hydrolyze dioxane gives a 32−48% overall yield (Table 2). The reaction has been run on a 6−9 kg scale and produced aldehyde **5** in greater than 97% purity as the bisulfite adduct (50−60% yield). The total process time for cross-coupling and deprotection on the 6−9 kg scale was less than 4 days.

Table 2. **Deprotection of 4-(4-benzyloxyphenyl)butanal acetal with formic acid**

acetal	time (hr)	overall combined steps-yield of isolated **5**
dioxane	24.0	48
dioxane	4.5	32
dioxolane	1.0	62
dioxolane	2.0	53

Conclusions

In summary, the feasibility of combining copper-mediated Grignard cross-coupling with in situ hydrolytic acetal deprotection in a scale-up process to prepare 4-(4-benzyloxyphenyl)butanal has been demonstrated. On scale-up this application of cross-coupling chemistry provided expected yields, economies in equipment utilization, and provided dependable quality product. In addition, the procedure allows for handling the labile γ-arylbutanal under conditions that minimize or eliminate dimerization or other degradation products. This processing methodology of combining cross-coupling with deprotection is being studied further to extend its utility to other applications.

Experimental Section

Materials. Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. All ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz with a GE Q300. The ^{1}H NMR and ^{13}C NMR chemical shifts are expressed as δ values (ppm) corrected to TMS internal standard.

General Procedure. In a typical reaction procedure adaptable to scale-up, the Grignard solution is prepared by adding 10.6 mL (90.4 mmol) of 2-(2-bromoethyl)-1,3-dioxolane in 80 mL of THF to 2.4 g (99 mmol) of magnesium turnings (during the induction period about 10% of the dioxolane solution is used). Intermediate **2** (Scheme

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2) is prepared at or below 30 °C.[8] The solution is cooled to 0 to −5 °C and treated with a solution containing 15.0 g (64.5 mmol) of 4-benzyloxybenzyl chloride in 80 mL of THF and 3 mL of 0.1 M Li_2CuCl_4 in THF. The dilithium tetrachlorocuprate solution is prepared by mixing 0.85 g (20 mmol) of lithium chloride and 1.34 g (10 mmol) of copper(II) chloride in 100 mL of THF at room temperature. The coupling reaction is stirred for 5 h at 0 to −5 °C and then allowed to warm to room temperature. The reaction is quenched with 1 M aqueous ammonium chloride (100 mL), maintaining the temperature below 35 °C. The mixture is diluted with ethyl acetate (100 mL) and washed with water (100 mL). The volume of the organics is reduced by 50% by vacuum distillation and filtered through a fulflo filter to remove bis-ether by-product **6**. The mixture is diluted with 30 mL of water and the remainder of the organic solvent distilled off under vacuum at 30−40 °C. The mixture is then charged with 40 mL of aqueous 80% formic acid and stirred for 1 h at 20−25 °C. The reaction is diluted with brine (100 mL) and extracted with methylene chloride (2 × 100 mL). Residual acid is removed by bicarbonate washes (2 × 100 mL) of the combined organic layers. The organic layer is concentrated by vacuum distillation and dissolved in 20 mL of 2-propanol. The solution is added to a solution of 16.0 g of sodium bisulfite in 50 mL of water, and warmed to 65 °C. Upon cooling, the bisulfite adduct of the product aldehyde crystallizes out and is collected and dried to afford 12.6 g (55%) of desired bisulfite product **5** (Scheme 2).

All compounds reported in this note exhibited ^{1}H NMR characteristics in agreement with their structures or matching published spectra.

4-(4-Benzyloxyphenyl) butanyl-1,3-dioxolane 3: ^{1}H NMR (DMSO-d_6) δ 7.48−7.27 (m, 5H), 7.00 (dd, J = 8.7, 52.7 Hz, 4H), 5.05 (s, 2H), 4.78 (t, J = 4.5 Hz, 1H), 3.89−3.68 (m, 4H), 2.5 (t, J = 6.9 Hz, 2H), 1.68−1.50 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 156.5, 137.2, 134.1, 129.2, 128.3, 127.7, 127.6, 114.5, 103.5, 69.1, 64.2, 34.0, 32.8, 25.7.

4-(4-Benzyloxyphenyl) butanal, 4: ^{1}H NMR ($CDCl_3$) δ 9.68 (t, J = 2.0 Hz, 1H), 7.50−7.22 (m, 5H), 6.96 (dd, J = 8.9, 51.7 Hz, 4H), 4.99 (s, 2H), 2.55 (t, J = 7.5 Hz, 2H), 2.35 (dt, J = 2.0, 7.5 Hz, 2H), 1.88 (quintet, J = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 202.1, 157.0, 137.0, 133.4, 129.2, 128.3, 127.7, 127.3, 114.6, 69.8, 42.9, 33.9, 23.6.

Bis-4-benzyloxybenzyl ether, 6: ^{1}H NMR ($CDCl_3$/CD_3-OD) δ 7.48−7.27 (m, 10H), 6.99 (dd, J = 8.4, 55.7 Hz, 8H), 5.05 (s, 4H), 2.82 (s, 4H). ^{13}C NMR ($CDCl_3$/CD_3OD) δ 156.8, 136.9, 134.1, 129.2, 128.3, 127.7, 127.3, 114.5, 69.9, 37.1. MS (CI, NH_3) m/z (relative intensity) 412 (M + 1, 100).

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