Organic Process Research & Development **2010**, *14*, 477–480

A Synthesis of 3,5-Disubstituted Phenols

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Abstract:

Robust and scalable syntheses of some synthetically useful 3,5-disubstituted phenols are presented. The process involves the selective displacement of a halogen by nucleophilic aromatic substitution using a preformed mixture of potassium *tert*-butoxide and *p*-methoxybenzyl alcohol (PMB−OH), followed by deprotection of the PMB ether with acid in the presence of 1,3-dimethoxybenzene. These processes have been demonstrated on kilogram scale, providing crystalline phenols in good yield and high purity.

Introduction

Phenols with the 3,5-substitution pattern can be synthetically challenging and are not widely available in significant quantities from commercial sources. As part of a research effort, we had need of a reliable synthesis of phenols of this type. Phenols **1** and **2** were identified early on as key starting materials.[1] Our medicinal chemistry colleagues were interested in further modifications at the 3- and 5-positions and so compounds **3** and **4** were chosen as they could easily be elaborated by taking advantage of various chemistries known for aryl halides.

Classically, phenols of this type have been prepared according to the method of Hodgson[2] by using diazonium chemistry. Various 1,3,5 substituted benzenes are currently available commercially, possibly from similar Sandmeyer type processes. Phenols **1**−**4** have become available from catalog vendors in the past few months indicating an increasing interest.

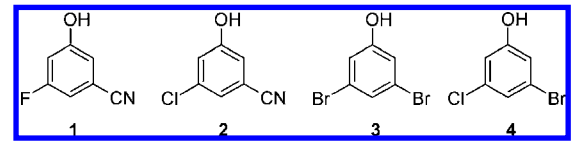
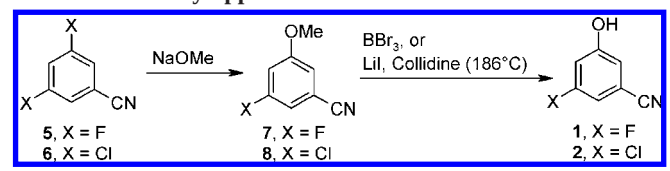


Figure 1. **3,5-Disubstituted phenols of interest.**

Scheme 1. **Early approaches to 1 and 2**



Although unknown to us at the outset of this work, recent progress in the transition metal catalyzed coupling of hydroxide has opened up the possibility of replacing halogens directly to access a variety of phenols and avoiding biaryl ether formation.[3] A recent report describing the preparation of **3** by C−H activation has also surfaced.[4] Notwithstanding, experimental details for larger scale syntheses, and more generally, descriptions of synthetic approaches readily amenable to scale-up are quite limited. Our requirements for phenols **1**−**4** ranged from hundreds of grams to >10 kg, and at the start of our effort there were few viable options.

Results and Discussion

Dichloro- and difluoro-benzonitrile **5** and **6** are commercially available, and **6** had been reported[5] to react selectively with sodium methoxide to displace one halogen (Scheme 1). The resulting methyl ether has been cleaved by either reaction with lithium iodide in collidine under reflux (186 °C), or with boron tribromide.[6]

This methoxide approach had a number of potential limitations. Boron tribromide, or the rather forcing conditions of lithium iodide in refluxing collidine were needed to remove the

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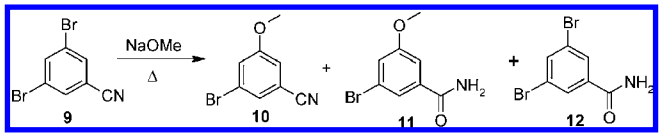
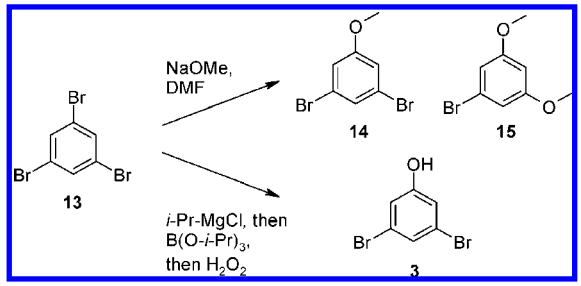
10.1021/op900322u
Published on Web 02/04/2010

Scheme 2. **Possible byproducts formed with 3,5-dibromo benzonitrile**



Scheme 3. **Byproducts in reaction with 1,3,5-tribromobenzene**



methyl group, and neither option was appealing for large scale work. The reaction of methoxide with 3,5-dibromo-benzonitrile (**9**) did not result in a clean transformation (Scheme 2). In order for methoxide to participate in a nucleophilic aromatic substitution with the more electron rich dibromide, a temperature of 50−80 °C was required. Unfortunately this temperature also increased the susceptibility of the nitrile group to nucleophilic attack, leading to a mixture of **10** and byproducts tentatively identified by LC/MS as amides **11** and **12**.

Also, while 1,3,5-tribromobenzene (**13**) did participate in the nucleophilic aromatic substitution reaction with methoxide in DMF at 80 °C, in our hands the reaction resulted in a mixture of either **13** and **14**, or **14** and **15** neither of which provided an opportunity for simple purification (Scheme 3).[6] Alternatively, it was shown that **13** could be treated with isopropylmagnesium chloride under mild conditions to give the *mono*-Grignard species rapidly and selectively.[7] Subsequent transmetalation with triisopropyl borate occurred on a similarly rapid time scale, also with a small exotherm. If the resulting aryl boronic ester solutions were oxidized with aq. hydrogen peroxide, then 3,5-dibromophenol was the main product. However, several other poly brominated phenols also formed and were detected by GC/MS as byproducts in the isolated material.

We hypothesized that the electron rich phenol would be highly susceptible to electrophilic aromatic substitution, and that the mixture of bromide ions and peroxide resulted in electrophilic bromine species capable of brominating **3**. We found that removal of volatile byproducts including isopropyl bromide, and the inorganic magnesium salts prior to the peroxide addition allowed 3,5-dibromophenol to be synthesized in high yield and purity without simultaneous production of poly brominated phenols. Thus, after Grignard formation, and addition of B(*i*-PrO)$_3$, the mixture was sequentially washed with dilute sulfuric acid, and then concentrated by distillation under reduced pressure. Then, when the oxidative peroxide treatment and workup was initiated, **3** was made cleanly. This process has been demonstrated on 50-g scale, providing a near quantitative yield of 3,5-dibromophenol with a single isolation. Although

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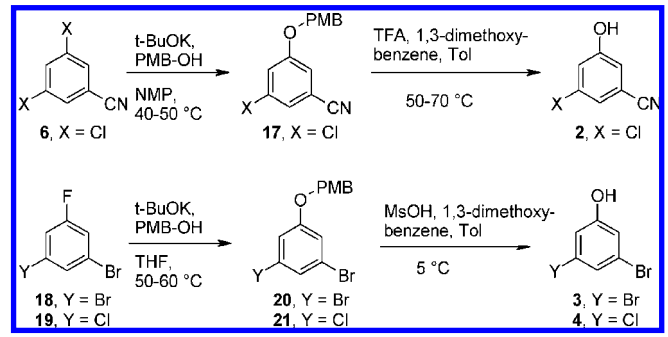
Scheme 4. **Scalable preparation of phenols 2−4**



the approach was not pursued for further scale up, it offers a very reasonable and rapid approach to lab scale production of **3**.

Looking back at phenol **2**, alternative alkoxide nucleophiles seemed likely to be effective and offer the benefit of a more facile cleavage. Tertiary alcoholates did not participate in the nucleophilic aromatic substitution, and potassium *tert*-butoxide turned out to be the preferred base for subsequent investigations. We quickly settled on 4-methoxybenzyl alcohol (PMB−OH) (Scheme 4).[8]

Reaction of **6** with a preformed mixture of 4-methoxybenzyl alcohol and potassium *tert*-butoxide, in a small volume of *N*-methyl-pyrrolidinone (NMP) provided the corresponding ether **17**. Attempts to execute this reaction in THF resulted in incomplete consumption of the starting benzonitrile. The nitrile functionality appeared to be more reactive in less polar media, and cyclotrimerization of the nitrile into 2,4,6-triazines[9] was observed by LC-MS. This behavior was sufficiently suppressed, but not eliminated in NMP. After the reaction was complete, the dark solution was cooled, and added to a mixture of toluene and dilute aqueous acetic acid. The organic layer was separated from the aqueous NMP[10] to give a solution of **17** in toluene ready for direct deprotection or isolation.

In order to access the bromo derivatives **3** and **4**, 1,3-dibromo-5-fluorobenzene (**18**) or 1-bromo-3-chloro-5-fluorobenzene (**19**) were used respectively. Carrying out the displacement was straightforward. Using 4-methoxybenzyl alcohol and potassium *tert*-butoxide, this time in THF at 50−60 °C, provided the corresponding ethers in good yields (>90% isolated solid). In these cases, isolation was generally carried out after aqueous workup, by replacing the solvent with methanol.

With these protected phenols in hand, a series of deprotection conditions were evaluated using **17** as a model because at the

(8) Other primary alcohols would be expected to participate in the nucleophilic aromatic substitution, thus opening up the possibility of allyl-, or 2-trimethylsilylethyl-protected phenols; however, such experiments were not tested in our lab.

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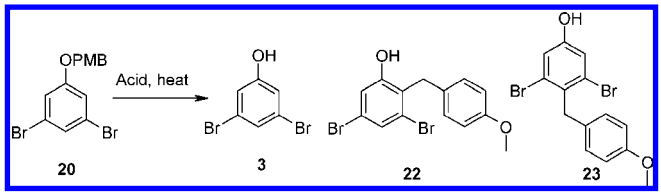
Scheme 5. **Byproducts were observed in the deprotection step for the electron rich 20**



time compound **2** was in high demand.[11] In acetic acid at or near 110 °C, deprotection was complete, but the formation of 4-methoxybenzyl acetate was problematic. Unfortunately, this byproduct acted as a cosolvent in the isolation resulting in only modest yields, and it was partly retained in the isolated product after crystallization. The use of stronger acids with less nucleophilic conjugate bases eliminated the formation of adducts of this type, but led to a mixture of polymeric material derived from the 4-methoxybenzyl group that coprecipitated with the product. For the electron rich phenols such as **20**, alkylated byproducts such as **22** and **23** (Scheme 5) were detected by LC/MS. It was clear that a cation scavenger was required.

To avoid the stench complications associated with the large scale use of sulfur-derived additives, other electron rich aromatics were explored as cation scavengers. The introduction of excess 1,3-dimethoxybenzene proved effective, decreasing the formation of alkylated byproducts related to the desired phenol to nearly undetectable levels in the isolated phenols.

Ultimately, two methods were found to be highly effective for the deprotection, each being suited to the nature of the specific compound. For ethers **20** and **21**, both of which were isolated intermediates, catalytic (10 mol %) methanesulfonic acid at 5 °C with 2.5 equiv of 1,3-dimethoxybenzene in a small volume of toluene was shown to be optimal. Upon reaction completion, the mixture was extracted with caustic to separate the phenol from the organic byproducts and solvents, and then crystallized by acidification resulting in yields generally of 80−85%.

In the case of **17**, obtained as a solution in toluene, a telescoped process was desired. However, the methanesulfonic acid catalyzed deprotection method required rigorous elimination of water and residual *p*-methoxybenzyl alcohol as these sequestered and/or consumed the catalytic acid. Trifluoroacetic acid (0.5 equiv) in toluene at 70 °C was employed, again using 1,3-dimethoxybenzene as a scavenger. Due to the observation that measurable amounts of nitrile hydrolysis could occur during the caustic extraction of **2**, an alternative purification was developed. First, the crude phenol product was precipitated from the toluene-TFA reaction mixture by addition of heptane. The product was isolated by filtration, and the wet-cake was dissolved in isopropanol. The isopropanol solution was then treated with activated carbon and filtered. The clarified solution was concentrated partially, and the solvent replaced with heptane to induce crystallization, and **2** was isolated in 75% overall yield from **6**.

(11) 3-Fluoro-5-hydroxybenzonitrile was not pursued further, and no procedure was demonstrated. However, it is highly likely that the developed procedure described for 3-chloro-5-hydroxybenzonitrile would be effective.

Conclusion

In summary, procedures for the formation of differentially 3,5-substituted phenols from inexpensive commercially available starting materials have been developed and demonstrated to be effective on a reasonable scale. Further improvements could be envisioned, including the possible elimination of intermediate ether isolations for **20** and **21**, and optimizing the final crystallization conditions, but these are unnecessary for general practice. These processes have been demonstrated on scales delivering between grams and kilograms of phenols as high purity crystalline solids where the yields were generally 75−85% overall for the process.

Experimental Section

Unless otherwise noted, solvents and reagents were reagent grade and used without purification. All reactions involving air or moisture-sensitive reagents were performed under an inert atmosphere of nitrogen. Unless otherwise stated, analytical HPLC separations were performed using an Agilent Zorbax SB-C8, 100 mm length × 3.0 mm ID packed with 3.5 μm particles, flow rate of 1.2 mL/min, and a linear gradient as follows: Component A: 0.1% trifluoroacetic acid in water; Component B: 0.1% trifluoroacetic acid in acetonitrile; elution gradient 10% to 90% B from 0 to 3.5 min, hold 90% B for 1.5 min, temp 30 °C, UV detection at 220 nm. Mass spectra were taken using an Agilent 6890N GC with an Agilent 5973N MS instrument using electron impact (EI) positive ionization energy = 70 eV [tuned with PFTBA (perfluorotributylamine)]. The column is an Agilent DB-5MS, 30 m length × 0.25 mm diameter, 0.25 μm film thickness. Oven is programmed from 70 to 300 °C at 20 °C/min. Injector temp = 250 °C.

3-Chloro-5-hydroxybenzonitrile (2). To a solution of potassium *tert*-butoxide (3 kg, 26.7 mol) in NMP (12 kg) was added 4-methoxybenzyl alcohol (4.22 kg, 30.5 mol) at <40 °C. The resulting mixture was stirred for 1 h and then transferred over 40 min into a premixed solution of 3,5-dichlorobenzonitrile (4.37 kg, 25.4 mol) in NMP (5 kg) at 40−50 °C. The reaction was stirred for 1.5 h at 40 °C, (at which point HPLC analysis showed **17** (rt 3.76 min) and <2% of dichlorobenzonitrile) and then cooled to 22 °C and quenched with a mixture of water (22 L), acetic acid (5 kg) and toluene (30 kg). The mixture was stirred vigorously and the aqueous layer removed. The organic layer was washed with additional water (3 × 20 L) and then concentrated by atmospheric distillation at 110 °C (removing ~20 kg solvent). The mixture was cooled to 50 °C, and 1,3-dimethoxybenzene (4.1 kg, 29.7 mol) and trifluoroacetic acid (1.5 kg, 13.2 mol) were added. The mixture was stirred at 70 °C for 2 h (HPLC analysis showed <2% **17**), at which point it was diluted with heptanes (26 kg) and then cooled to 5 °C overnight. The precipitate was filtered and then washed with heptanes (20 kg) and dried under N_2. The damp, crude cake (86.4% purity by HPLC/external standard) was combined with Celite (600 g) and Calgon activated carbon (600 g) in isopropanol (20 kg) and the suspension stirred at 80 °C for 2 h. The mixture was cooled to 22 °C and then filtered through a Celite pad. The cake was rinsed with additional isopropanol (10 kg). The combined filtrate was partially concentrated by distillation under reduced pressure to approximately 1/2 the original volume,

and then the solvent was replaced with heptane (~35 kg total) to maintain this volume until an atmospheric pressure distillation pot temperature of ~93−96 °C was observed. The mixture was slowly cooled to 0 °C over 18 h, the thick suspension was filtered, the cake washed with additional heptane (10 kg), and dried at 60 °C for ~6 h (a sample showed 0.49% LOD). 3-Chloro-5-hydroxybenzonitrile was isolated as 2.94 kg (75.1% yield) of an off-white solid: mp 165−166 °C; ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 7.23 - 7.22 (m,. 1H), 7.10 - 7.09 (m, 1H), 7.03 - 7.01 (m, 1H), 5.36 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d6) δ (ppm) 159.25, 135.02, 122.53, 120.93, 118.12, 113.83; mass spectrum (EI) *m*/*z* 153 (M+ base), 155. AN HPLC retention time 2.66 min, purity of 96 wt % (external standard).

3-chloro-5-(4-methoxy-benzyloxy)benzonitrile 17. A small portion of the toluene extract from above was concentrated to a glass under reduced pressure, then dissolved in refluxing ethanol, filtered and cooled to 5 °C to give **17** as a white solid: mp 85−86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.31 (d, J = 9.0 Hz, 2 H) 7.08 − 7.11 (m, 1 H) 7.01 (dd, J = 2.3, 1.5 Hz, 1 H) 6.88 − 6.94 (m, 3 H) 4.93 (s, 2 H) 3.81 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.90, 159.76, 135.55, 129.30, 127.80, 123.93, 122.85, 116.88, 114.49, 114.14, 70.38, 55.32; mass spectrum (EI) *m*/*z* 273 (M+), 153, 121 (base).

3,5-dibromophenol (3). 4-Methoxybenzyl alcohol (86.5 g, 626.23 mmol) was warmed to liquefy (26 °C) and added over 20 min to a slurry of potassium tert-butoxide (69.6 g, 620.32 mmol) in THF (525 mL, 3.5 volumes) at ambient temperature, the resulting exotherm raised the reaction temperature to ~ 40 °C The mixture was stirred for 30 min at 40 °C and then dibromofluorobenzene (150 g, 591 mmol) was added over 20 min. An exotherm up to ~60 °C was observed and the mixture was stirred at 60 °C for 2 h (at which point HPLC analysis showed <3% dibromofluorobenzene). The mixture was cooled to ambient temperature and allowed to stand overnight. It was then diluted with water (200 mL) and acetic acid (4.5 g) and the layers separated. The aqueous layer was washed with ethyl acetate (100 mL) and the combined organic fraction was washed with 50% saturated brine and concentrated under vacuum to an oil. The crude oil was slurried with vigorous stirring in methanol (300 mL) at 50 °C and then cooled to ambient temperature overnight. The precipitate was filtered and washed with methanol (2 × 50 mL), air-dried and then vacuum oven-dried at 50 °C. Ether **20** was obtained as 204.1 g (93% yield) of white solid, HPLC retention time 4.15 min, with AN HPLC purity of 97.8%: mp 58−60 °C, ^{1}H NMR (300 MHz, $CDCl_3$)) δ ppm 7.31 (d, J = 8.7 Hz, 2 H) 7.22 − 7.27 (m, 1 H) 7.05 (d, J = 1.5 Hz, 2 H) 6.91 (d, J = 8.7 Hz, 2 H) 4.93 (s, 2 H) 3.81 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 159.98, 159.76, 129.32, 127.77, 126.60, 123.10, 117.35, 114.14, 70.38, 55.32; mass spectrum (EI) *m*/*z* 372 (M+), 252, 121 (base).. Ether (**20**) (150 g, 403.16 mmol) was dissolved in toluene (150 mL, 1 vol) and 1,3-dimethoxybenzene (150 mL, 1 vol) and cooled to 5 °C. Methanesulfonic acid (3.87 g, 40.32 mmol) was added over 15 min at <10 °C. After stirring for an additional 5 min the reaction was deemed complete by AN HPLC analysis (<1% **20** detected). The mixture was diluted with water (120 mL) and the pH was adjusted to ~11−11.5 with 50% KOH solution and the layers separated after vigorous stirring. This caustic extraction process was repeated three times and the combined aqueous fractions washed with toluene (80 mL) and then filtered through cotton. Acidification at ambient temperature to a pH of ~1.5 produced a slurry that was aged for 30 min, filtered, and washed with water. Air drying followed by vacuum oven drying at 50 °C produced 85.5 g (84% yield based on ether **20**, and 78% overall) of 3,5-dibromophenol[12] as a white solid, HPLC retention time 3.70 min, AN HPLC purity of 99.65%.

Alternative 3,5-Dibromophenol Synthesis (3). To a degassed, stirring solution of 1,3,5-tribromobenzene (50 g, 159 mmol) in toluene (250 mL) at 20 °C, was added *i*-PrMgCl (103 mL, 206 mmol, 2 M in THF) over 5 min with the use of an ice bath to keep the temperature of the mixture below 25 °C. After reaction was complete, the mixture was stirred for 10 min at 20 °C, then, tri-isopropyl borate (39 g, 48 mL, 206 mmol) was added over 10 min at <30 °C. After the addition was complete the mixture was stirred for 10 min and aqueous sulfuric acid (170 mL, 10 wt %) was added slowly at <40 °C. The aqueous layer was separated, and the organic layer was washed with water (50 mL). The toluene solution was cooled to 5−10 °C and concentrated by distillation under reduced pressure (30−50 Torr), until the volume of the solution decreased by about half. Foaming and bumping during the distillation was noted and a nitrogen inlet was used in the early part of the distillation to minimize the foam. After distillation, the concentrated solution was stirred and aqueous hydrogen peroxide (22 g, 30% H_2O_2 in water) was added slowly at <50 °C. The beginning of this addition was very exothermic. After the addition was complete, water (200 mL) was added and the mixture stirred vigorously. The phase separation took 10−15 min, and the aqueous phase resided on top of the mixture. The organic layer was washed with an additional 50 mL water, and the combined aqueous mixtures were extracted with toluene (50 mL). The combined toluene solution was then concentrated to an oil under reduced pressure and distilled using a Kugelrohr apparatus, temperature 160−170 °C, 20−25 Torr, to give 40 g of **3**[12] which solidified in the receiver flask.

3-Chloro-5-(4-methoxy-benzyloxy)bromobenzene (21). Prepared in 93% as described for **20**, starting from 3-chloro-5-fluoro-bromobenzene, and isolated as a white solid from methanol, HPLC retention time 4.11 min, mp 49−50 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.32 (d, J = 9.0 Hz, 2 H) 7.21 − 7.24 (m, 6 H) 7.18 (t, J = 2.1 Hz, 1 H) 7.09 − 7.11 (m, 1 H) 6.93 (d, J = 9.0 Hz, 2 H) 5.00 (s, 2 H) 3.83 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.93, 159.60, 136.03, 129.33, 127.21, 124.31, 120.44, 117.47, 116.75, 114.27, 70.67, 55.34; mass spectrum (EI) *m*/*z* 326 (M+), 328, 121 (base).

3-Bromo-5-chloro Phenol (4). prepared in 81% yield according to the procedure for **3**, giving an off white solid, HPLC retention time 3.10 min, mp 68−69 °C,[13] in 75% overall yield from 3-chloro-5-fluoro-bromobenzene.

Acknowledgment

Significant analytical support for this work was provided by Frida Dobrouskin, Tim Lane, Ashraf Abdallah, and Tina Nguyen, and we thank them for their efforts.

Received for review December 10, 2009.

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(12) Product matched the spectral properties given in ref 4.
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