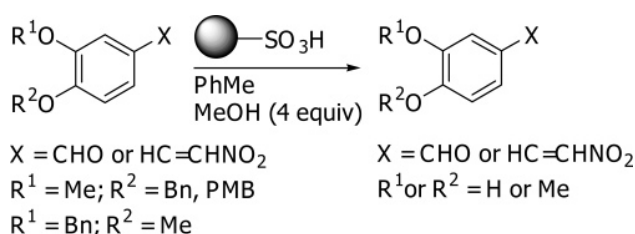


Solid-Supported Acids for Debenzylation of Aryl Benzyl Ethers

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Solid-supported acids have been investigated for aromatic debenzylation reactions. Stoichiometric amounts of solid-supported acids in refluxing toluene with or without 4 equiv of methanol effectively provided the desired aromatic debenzylation products of various systems in moderate to excellent yields (up to 98%).

The development and utility of solid-supported reagents in organic synthesis have been well documented over a number of years as they have found wide application by serving as reagents, catalysts, or scavengers.¹ In principle, these polymer-

bound materials can be economically recycled. Their use in organic synthesis simplifies the reaction procedures, as these reactions generally require simple filtration to remove the polymer-bound materials without the necessity of aqueous workup, resulting in less aqueous and organic waste than otherwise generated from the workup procedure. Consequently, development and use of polymer-supported reagents in various reactions are crucial for practicing green chemistry. In addition, reactions employing solid-supported reagents can be analytically monitored in a manner similar to those using other conventional reagents.

A number of protecting groups for phenol have been developed and used extensively in organic synthesis for many years.² The benzyl group and its derivatives have been employed as hydroxy-protecting groups for their ease of preparation and removal and their chemical stability toward a number of reaction conditions. Their versatility makes them ideal for protecting group manipulation. In general, conditions employed for aromatic debenzylation fall into the categories of (1) catalytic hydrogenolysis³ (H_2 in the presence of Pd/C or Raney Ni), (2) reductive cleavage⁴ (Na or Ca in NH_3), (3) iodide-mediated debenzylation⁵ (TMSI or NaI in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$), (4) metal-mediated debenzylation⁶ (TiCl_3 in the presence of Mg), (5) Lewis-acid-mediated debenzylation⁷ ((a) AlCl_3 in the presence of *N,N*-dimethylaniline or (b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in the presence of (1) ethanethiol or (2) 2-bromo-1,3,2-benzodioxaborole), and (6) acid-mediated cleavage⁸ ((a) $\text{CF}_3\text{CO}_2\text{H}$ in the presence of (1) thioanisole and/or $\text{CH}_3\text{OSO}_3\text{F}$ or $\text{CF}_3\text{OSO}_3\text{F}$ and (2) pentamethylbenzene or (b) concentrated HCl in refluxing EtOH). Each method offers its own advantages but possesses some limitations. As a result, there still exists a need for developing new methods for aromatic debenzylation.

Our interest in developing a new method for aromatic debenzylation arises in part from our synthetic program for lamellarins (**1**) whose structures contain substituted polyoxy-genated aromatics on their periphery. Two of our synthetic approaches⁹ for lamellarins require substituted benzyl-protected aromatic synthons **2–5** (Scheme 1). In addition, we have

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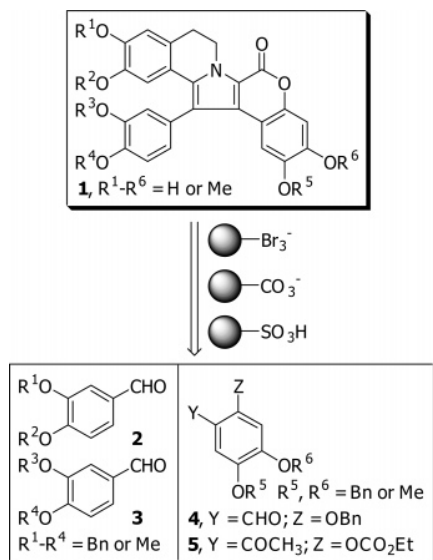
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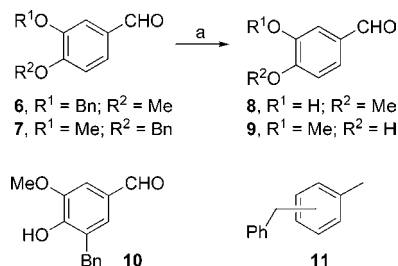
SCHEME 1. Substituted Benzyl Ethers of Aromatic Synthons 2–5



investigated the utility of solid-supported reagents in two synthetic approaches developed by our group. We have shown that three polymer-supported reagents could be employed sequentially for the synthesis of either natural or unnatural lamellarins.^{9d} During this work, we have encountered a novel Amberlyst-15-mediated aromatic debenzylolation reaction. We now wish to report the results of our investigation of this aromatic debenzylolation reaction employing solid-supported acids.

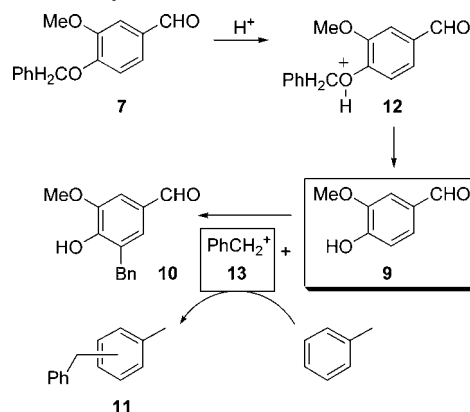
Because the basic units required for the synthesis of lamellarins are the substituted benzaldehyde derivatives whose aromatic hydroxy groups were protected as benzyl, the systems we first investigated were the benzyl ethers of isovanillin **6** and vanillin **7**. Their preparation employed a standard benzylation reaction with K_2CO_3 serving as base in refluxing acetone and benzyl bromide as the benzylating agent.¹⁰ Such reaction conditions provided the corresponding benzyl ether products in excellent yields (86–98%). With the starting materials in hand, we first explored aromatic debenzylolation using 3 equiv of Amberlyst-15, a sulfonic acid on polymer support, in toluene at 110 °C for 2 h, which were the conditions previously employed in the synthesis of the lamellarin framework.^{9d} Isovanillin and vanillin were obtained from **6** and **7** in 57% and 75% yields, respectively. Aromatic debenzylolation of **7** was thus chosen for a more detailed study because of its significantly higher yield. Examination of the reaction mixture showed that C-benzylated vanillin **10** was formed in 23% yield. In addition, Friedel–Crafts-type benzylation of the solvent toluene gave rise to an inseparable mixture of presumably ortho- and para-benzylated toluene **11** (Scheme 2).

The parameters we have investigated and optimized for solid-supported acid in aromatic debenzylolation were (1) the amount

SCHEME 2. Aromatic Debenzylation^a of Benzyl Ethers **6** and **7**

^a Reagents and conditions: (a) Amberlyst-15 (3 equiv), toluene, 110 °C, 2 h, 57% (**8**), 75% (**9**), 23% (**10**).

SCHEME 3. Proposed Mechanism of Acid-Mediated Aromatic Debenzylation



and type of solid-supported acids (Amberlyst-15, Lewatit, Dowex 2030, and Dowex 50X), (2) the temperature, (3) the effect of solvents, and (4) the effect of different benzyl scavengers (bromoanisole, thioanisole, and methanol) as additives. It was found that all solid-supported acids utilized in this study except Dowex 50X were effective in aromatic debenzylolation. A stoichiometric amount of solid-supported acid was required for complete consumption of starting material. Lowering the temperature may improve the product ratios but result in a longer reaction time. The best solvent was found to be toluene. Our proposed reaction mechanism, which involves initial protonation at the oxygen atom followed by C–O cleavage to generate the corresponding benzylic carbocation **13** along with the desired phenol and quenching of the benzyl cation with toluene, reasonably suggested that the formation of **10** could partly arise from the intermolecular benzylation of vanillin under this reaction condition (Scheme 3) and prompted us to consider the use of benzyl scavengers as additives that could scavenge the benzyl cation faster than vanillin to suppress the formation of **10**. Among the benzyl scavengers employed in this study, we found that a mixed solvent system of 4 equiv of methanol in toluene gave the best result, providing the desired product vanillin in excellent 98% yield with only trace amounts of C-benzylated vanillin **10**. Larger amounts of methanol (10:1 by volume) resulted in no reaction presumably because of the competing initial protonation between the substrate and the methanol. (For full details of optimization for aromatic debenzylolation of **7**, see the Table and the following discussion in the Supporting Information.)

The electronic nature of the benzyl group toward debenzylolation was also investigated. Compounds **14**–**16** (Figure 1) were

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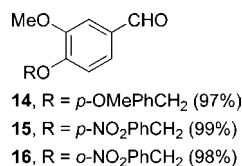


FIGURE 1. Structure of PMB, PNB, and ONB ethers of vanillin **14**–**16**.

synthesized from the corresponding substituted benzyl halides in the presence of K₂CO₃ as base in 97–99% yields.^{11,12} The electron-donating *p*-methoxy group is expected to favorably stabilize the positive charge on the benzylic carbon, and the electron-withdrawing *o*- or *p*-nitro group would destabilize such charge on that position. We then anticipated that the *p*-methoxy benzyl group (PMB) would undergo a more facile aromatic debenzylolation reaction, whereas a similar reaction for the *o*-nitro benzyl (ONB) or *p*-nitro benzyl (PNB) group would require harsher conditions.

After some experimentation, we found that aromatic debenzylolation of PMB ether required 5 equiv of Amberlyst-15 in toluene at 110 °C for 6 h and gave cleanly the desired product in 61% yield without any corresponding C-benzylated byproduct.¹³ In the presence of 4 equiv of methanol, only 2.2 equiv of Amberlyst-15 was required and the reaction proceeded to give the desired product **9** in 86% yield without any detectable amount of the C-benzylated product. The result suggested that the PMB cation is more stabilized and more selective toward nucleophilic attack. Under the reaction conditions, the presence of a PMB toluene adduct and the absence of the C-benzylated byproduct reflected the more effective quenching of the PMB cation by toluene than by vanillin. In addition, the improved yield with the added methanol further confirmed the results obtained from aromatic debenzylolation reactions of benzyl ether **7** and could be attributed to the lower equivalent of the acid employed, the presence of methanol, or both effects.

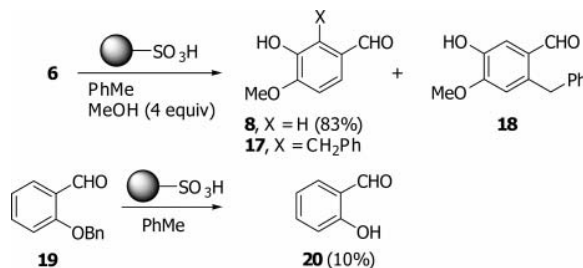
It is, however, perplexing to observe the longer reaction time for cleaving PMB ether in comparison with that for normal benzyl ether. It is less conceivable to propose that the rate of C–O cleavage of PMB ether is slower than that of benzyl ether because the resulting cation of PMB is more stabilized by the presence of the *p*-methoxy group. Thus, we propose that the longer reaction time for cleaving PMB ether is a consequence of the slower rate of quenching the resulting less reactive PMB cation by toluene. Our proposed explanation was confirmed by competitive debenzylolation reactions between vanillin benzyl ether **7** and PMB ether **14**.¹⁴ In the presence of both ethers in 1.1 equiv of Amberlyst-15 in toluene at 110 °C for 20 h, only the PMB ether was selectively cleaved (>95% conversion)

(11) *para*-Methoxy benzyl ether **14** was synthesized from vanillin (1.5 equiv), *p*-methoxy benzyl chloride (1.0 equiv), and K₂CO₃ (1.5 equiv) in the presence of *n*-Bu₄NI (0.2 equiv) in refluxing acetone, and the *para*- and *ortho*-nitro benzyl ethers **15** and **16** were prepared from vanillin (1.0 equiv), the corresponding nitro benzyl bromide (1.1 equiv), and K₂CO₃ (1.5 equiv) in refluxing acetone.

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(13) A number of other reaction conditions employing 1.1–3.0 equiv of Amberlyst-15 in toluene at 110 °C for 3–6 h gave **9** together with some detectable amount of **10**. When 5 equiv was used and the reaction time was less than 6 h, the reaction did not proceed to completion and the formation of **10** was observed. Interestingly, *p*-TsOH (1.5 equiv) under similar reaction conditions for 3 h effectively cleaved the PMB ether and only a trace amount of **10** was observed in the crude mixture.

SCHEME 4. Aromatic Debzylolation of Benzyl Ethers **6** and **19**



whereas benzyl ether remained intact (virtually 100%); no C-benzylated byproduct was observed. The result confirmed that the rate of C–O cleavage of PMB ether is indeed faster than that of benzyl ether. The overall longer reaction time reflected the time required for the most thermodynamically favorable pathway which includes initial protonation and quenching of the resulting cation with an available nucleophile. Excess acid (2.2 equiv) with similar length of reaction time resulted in cleavage of the benzyl ether as well.¹⁵ With 4 equiv of methanol, the reaction proceeded to selectively cleave PMB ether **14** in 6 h, providing **9** in quantitative yield without any C-benzylated byproduct, and 93% yield of benzyl ether **7** was recovered. It is noteworthy that various acid-mediated conditions, e.g., *p*-TsOH, TFA, and Amberlyst-15, were not effective in cleaving either ONB or PNB ethers.¹⁶

We then applied the optimized reaction conditions for aromatic debenzylolation reactions of other systems (Scheme 4). With 4 equiv of methanol, isovanillin benzyl ether **6** gave the desired product **8** in 83% yield along with *ortho*- and *para*-C-benzylated vanillin **17** and **18** in 10% combined yield.¹⁷ The formation of **18** further confirmed the proposed intermolecular mode of C-benzylation under these reaction conditions. We found that, even with the optimized reaction conditions, salicylaldehyde benzyl ether **19** gave the desired product **20** in only 10% yield along with C-benzylated byproducts.¹⁸

We then turned to the nitrostyrene system which is chemically prone to metal-mediated reduction/hydrogenation frequently and is similarly employed in hydrogenolysis of aromatic debenzylolation (Scheme 5). Nitrostyrene benzyl ethers **21** and **22** were prepared from the Henry reaction of **8** and **9** with nitromethane.^{9c} In the absence of methanol, nitrostyrene benzyl ether **21** gave cleanly the desired product **23**¹⁹ in 69% yield together with the

(14) The crude reaction mixture was analyzed by ¹H NMR. Piperonal was used as an internal standard, and the amount of the remaining starting material was determined by relative integration.

(15) Approximately 83% of benzyl ether was consumed.

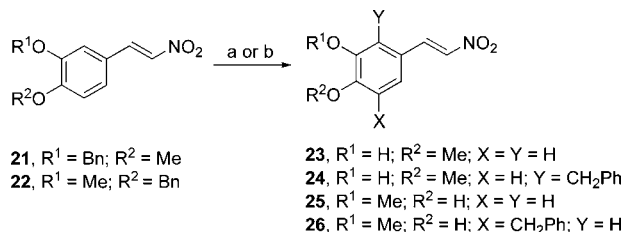
(16) After some experimentation, we found that ONB and PNB ethers were effectively cleaved by potassium *tert*-butoxide in refluxing *tert*-butyl alcohol. Vanillin was obtained in 84% and 80% yields from **15** and **16**, respectively. See Supporting Information for details.

(17) Without methanol, the reaction gave **8** in 57% yield as well as **17** and **18** in 12% combined yield.

(18) Compound **19** and **20** are commercially available (Aldrich). The low yield of salicylaldehyde may arise from its instability under reaction conditions. In a separate experiment, only 11% of salicylaldehyde was recoverable when treated with Amberlyst-15 in toluene at 110 °C for 4 h. The C-benzylated byproducts were generated in approximately 15% combined yield presumably as a mixture of 3-benzyl- and 5-benzyl-salicylaldehydes.

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SCHEME 5. Aromatic Debenzylation Reaction^a of Nitrostyrene Benzyl Ethers **21 and **22****



^a Reagents and conditions: (a) Amberlyst-15, toluene, 110 °C, 69% (**23**), 19% (**24**), 63% (**25**), 9% (**26**); (b) Amberlyst-15, toluene, methanol (4 equiv), 110 °C, 80% (**23**), 19% (**24**), 75% (**25**), 13% (**26**).

corresponding ortho-C-benzylated nitrostyrene phenol **24** in 19% yield. With 4 equiv of methanol, the reaction improved to give the desired product in 80% yield. Similarly, nitrostyrene **22** gave the corresponding products **25**¹⁹ in 63% yield and C-benzylated nitrostyrene **26** in 9% yield in the absence of methanol. With 4 equiv of methanol, the desired product **25** was obtained in 75% yield together with **26** in 13% yield. Therefore, these reaction conditions are chemically compatible with the nitrostyrene moiety.

In summary, we have developed and demonstrated a novel use of solid-supported acids for aromatic debenzylation reactions. The optimized reaction conditions were found to be Amberlyst-15 in toluene at 110 °C with 4 equiv of methanol as the benzyl scavenger. When compared with other previously reported methods of acid-mediated aromatic debenzylation, our optimized conditions offer several advantages. The conditions are compatible with some functional groups such as the nitrostyrene which is susceptible to hydrogenation and/or reduction conditions otherwise frequently employed for aromatic debenzylation reactions. In addition, the procedure is simple as

it requires only filtration to remove the polymer from the crude mixture, resulting in less organic as well as aqueous waste from the reaction. Taken together, use of solid-supported acids in the aromatic debenzylation reaction represents an approach suitable for practicing green chemistry and thus should find wide applications in protecting group manipulation.

Experimental Section

Aromatic Debenzylation Reaction Using **7 as an Example (Supporting Information, Entry 6, Table 1).** To a solution of vanillin benzyl ether **7** (0.021 g, 0.087 mmol) in toluene (3.5 mL) at room temperature was added Amberlyst-15 (0.021 g, 0.096 mmol). The resulting mixture was heated to 80 °C for 6 h. At that time, the reaction was cooled to room temperature and filtered and the polymer was washed with DCM and EtOAc. The solution was then concentrated under reduced pressure. The crude material was purified by preparative thin-layer chromatography (PTLC) to give the desired product vanillin **9** (0.012 g, 0.079 mmol, 89%), the C-benzylated product **10** (0.002 g, 0.008 mmol, 9%), and benzyl toluene adduct **11**.²⁰

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Supporting Information Available: General methods, experimental procedures, spectroscopic data, and copies of ¹H and ¹³C NMR of all new compounds (**10**, **11**, **17**, **18**, **24**, and **26**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(20) For complete characterization of compound **10** and **11**, please see the Supporting Information.