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# Synthesis of aryl ethers from aminoalcohols using polymer-supported triphenylphosphine

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**Abstract**—Optimum conditions for the preparation of aryl–alkyl ethers from *N*-protected aminoalcohols using polymer-supported triphenylphosphine have been developed. In contrast to previous literature reports, it was discovered that the progress of this reaction is greatly improved when a tertiary amine base is employed, along with minor modifications being made to the order of reagent addition. 

The Mitsunobu reaction has become a valuable synthetic method in organic chemistry over the past two decades.[1] However, a drawback of the approach, which has implications for parallel synthesis, is the concomitant formation of triphenylphosphine oxide. A number of procedures geared towards efficient removal of this by-product have recently been developed. Solid-phase Mitsunobu syntheses have become established synthetic protocols over the past 5 years; here, product purification is facilitated by washing away triphenylphosphine oxide and excess reagents from the resin-bound product.[2] Additionally, for solution chemistry, polymer-supported triphenylphosphine has been examined; upon completion of the reaction, triphenylphosphine oxide remains bound to the resin, enabling the desired products to be isolated cleanly by filtration.[3]

As part of our investigations into a targeted combinatorial library, we chose to study the synthesis of aryl–alkyl ethers using a solution-based Mitsunobu coupling approach with polymer-supported triphenylphosphine.[4] As an initial point of reference, we examined the method developed by Georg and co-workers, who had shown that phenols and alcohols could be combined in the presence of supported triphenylphosphine in dichloromethane, and then treated with diethyl axodicarboxylate to furnish the desired aryl–alkyl ethers in high purities and yields.[3] Our efforts centered on the Mitsunobu coupling of phenols with *N*-Boc-protected aminoalcohols. However, when we treated a collection of phenols with *N*-Boc-(D)-prolinol using the conditions reported by Georg, we observed poor conversion to the desired products; further, in each case, HPLCMS analysis of the products indicated the presence of multiple components.[5]

Subsequently, we conducted a statistically designed series of experiments in an effort to optimize the original reaction conditions. Anhydrous conditions were employed, the reaction temperature was varied, and alternative solvents were used; additionally, the effect of swelling the supported reagent prior to addition of the other reactants was studied, and alternative azodicaboxylates were employed. Disappointingly, in all cases we were unable to isolate the desired products in sufficiently acceptable yields and purities.

We did, however, obtain some encouraging results when a tertiary amine base was used as an additive. Further, we noted improvements in the progress of the reactions when the order of reagent addition was modified, and when aminoalcohols with benzyl protecting groups were used. Table 1 lists a representation of our results using three synthetic approaches: two routes developed by ourselves, conducted in the presence and absence of base (methods A and B, respectively),[6] and the conditions reported by Georg (method C). All of the reactions were conducted on a scale of 25 mg of protected aminoalcohol.[7]

Initially, we found that Mitsunobu coupling of *N*-benzyl protected aminoalcohols using Georg's approach proceeded with excellent conversion; further, we noted improved product purities when supported triphenylphosphine and diethylazodicarboxylate were first combined 0°C, followed by addition of a mixture of aminoalcohol and phenol (Table 1, entries 1–4).

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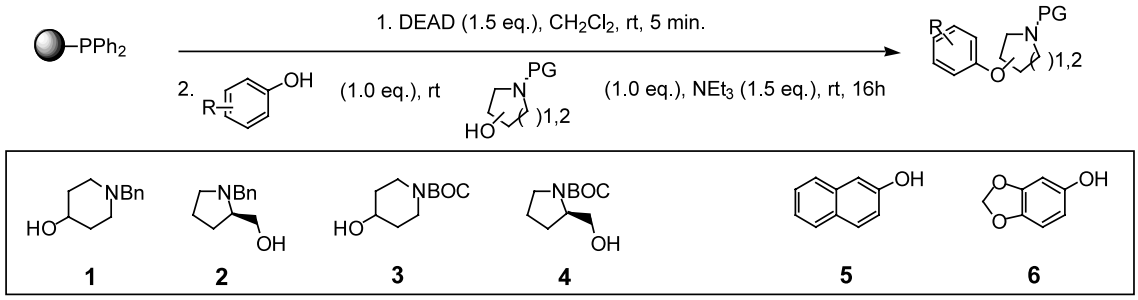
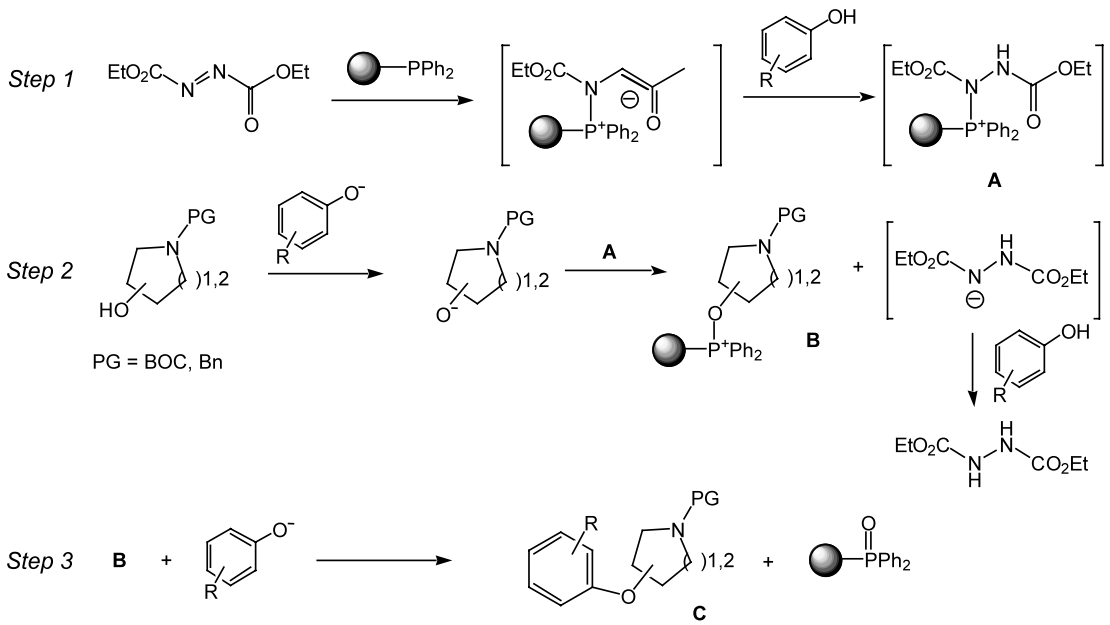
**Table 1.**




| Entry | Aminoalcohol | Phenol | Method | % Conversion[5] |
|---|---|---|---|---|
| 1 | 1 | 5 | A | 72 |
| 2 | 1 | 6 | A | 64 |
| 3 | 2 | 5 | A | 68 |
| 4 | 2 | 6 | A | 98 |
| 5 | 3 | 5 | A | 15 |
| 6 | 3 | 5 | B | 61 |
| 7 | 3 | 6 | C | 49 |
| 8 | 3 | 6 | B | 75 |
| 9 | 4 | 5 | C | 34 |
| 10 | 4 | 5 | B | 75 |
| 11 | 4 | 6 | C | 16 |
| 12 | 4 | 6 | B | 99 |

Intrigued by the possible influence of the basic tertiary amine on the progress of the reaction, we then conducted a series of experiments using the corresponding Boc-protected aminoalcohols, this time adding triethylamine (1.5 equiv.) to the mixture of phenol and aminoalcohol. Under these conditions, we observed good conversion to the desired products (Table 1, entries 6, 8, 10 and 12);[8] this was in sharp contrast to the results we obtained when additive base was not employed (Table 1, entries 5, 7, 9 and 11).

A study of the mechanism of the Mitsunobu esterification reaction has previously been conducted by Hughes and co-workers,[9] and we believe that their conclusions help explain the results of our own investigations. Scheme 1 summarizes the three steps involved in the etherification process. The first step, leading to the formation of the quaternary phosphonium adduct **A**, proceeds more rapidly than the subsequent steps. In order for activation of the protected aminoalcohol to occur to form the alkoxyphosphonium salt **B** in Step 2,




**Scheme 1.**

the hydroxyl group must first be deprotonated prior to the transfer of supported triphenylphosphine. The phenolate, generated in Step 1, deprotonates the aminoalcohol, and hence a key factor governing the rate of formation of **B** is the basicity of the phenolate. In cases where the phenolate is moderately basic, triethylamine assists in catalyzing Step 2; further, triethylamine promotes the subsequent formation of the phenolate for the $S_N2$ nucleophilic attack at **B** in Step 3, leading to the desired product **C**, and thereby enabling an overall enhanced rate of reaction. It is conceivable that the basic, *N*-benzyl protected tertiary aminoalcohol substrates serve similar catalytic roles to triethylamine in this process.

In summary, we have discovered that the solution-based Mitsunobu etherification of *N*-protected aminoalcohols using polymer-supported triphenylphosphine is improved in the presence of a basic tertiary amine, and also when the supported reagent is initially treated with diethylazodicarboxylate followed by addition of a combination mixture of the additional reagents. Aryl–alkyl ethers are produced cleanly and rapidly under these conditions.

## Acknowledgements

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## References

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4. Commercially available from Sigma Aldrich, catalogue number 36,645-5; loading of 3.0 mmol phosphorous per gram.
5. Percentage conversion to the desired products was determined by HPLC at 220 and 254 nm using an Agilent 1100 LC/MSD VL ESI system.
6. Typical procedure for method A: triphenylphosphine on polystyrene (1.5 equiv.) was treated with diethylazodicarboxylate (1.2 equiv.) at 0°C. Following agitation at this temperature for 5 min, the suspension was treated with a mixture of *N*-Boc-aminoalcohol (1.0 weight) and phenol (1.0 equiv.), and was then agitated at room temperature for a further 16 h. The suspension was filtered under reduced pressure; the filtrate was collected, evaporated under reduced pressure, and dried to furnish the desired product. Method B is identical to Method A, except triethylamine (1.5 equiv.) is added to the aminoalcohol and phenol mixture.
7. This reaction was repeated in some, but not all cases, on a scale of 825 mg of protected aminoalcohol, with similar percentage conversion to aryl–alkyl ether final product being observed.
8. The effect of *N*-methylmorpholine on the progress of solid-phase Mitsunobu etherification has been reported, see: Richter, L. S.; Gadek, T. R. *Tetrahedron Lett*. **1994**, *35*, 4705.
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