

Polymer-Bound Triphenylphosphine as Traceless Reagent for Mitsunobu Reactions in Combinatorial Chemistry: Synthesis of Aryl Ethers from Phenols and Alcohols

Ashok Rao Tunoori, Dinah Dutta, and Gunda I. Georg*

Department of Medicinal Chemistry and the Drug Discovery Program, Higuchi Biosciences Center, University of Kansas, Lawrence, KS 66045, USA

Received 18 August 1998; accepted 18 September 1998

Abstract: The synthesis of aryl ethers from phenols and alcohols using polymer-bound triphenylphosphine and diethyl azodicarboxylate (DEAD) is described. The polymer-bound triphenylphosphines are easily removed by filtration from the reaction products. This method is operationally simple and provides the products with high purity and in good yields.

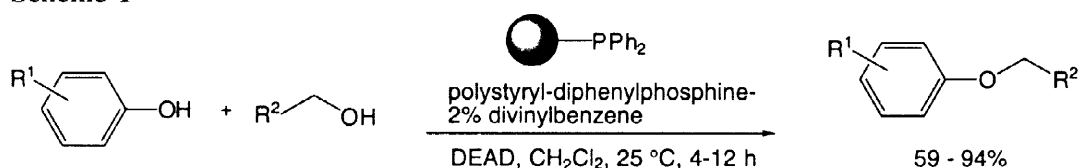
© 1998 Elsevier Science Ltd. All rights reserved.

Combinatorial chemistry^{1,2} has emerged as an important tool for the rapid synthesis of structurally diverse small molecule libraries and has therefore become highly important for drug discovery in recent years.^{3,4} Most libraries are generated through solid-phase synthesis,^{5,6} but solution-phase chemistry is receiving increasing attention.^{3,7,8} Synthetic chemistry methods, operating at the interface of solution- and solid-phase chemistry are also powerful tools in library generation. Examples are soluble polymers,⁹ support-bound sequestration reagents,¹⁰ or support-bound reagents.¹ The advantages of support-bound reagents over their soluble counterparts are their ability to drive the reaction to completion by using them in excess and the ease of their separation from the desired product by simple filtration.

The Mitsunobu reaction is a versatile and widely used reaction in organic synthesis.^{11–13} In a typical Mitsunobu reaction, a primary or secondary alcohol is esterified with a carboxylic acid in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine. Other acidic compounds, such as phenols can also be used in this reaction.^{12,13} A significant drawback of the Mitsunobu reaction is the need to remove excess triphenylphosphine, triphenylphosphine complexes, and the by-product triphenylphosphine oxide by chromatography for product purification. The Mitsunobu reaction has also been carried out on solid support.¹ These reactions are more easily purified than the solution-phase reactions because the phosphines can be removed by filtration from the polymer-bound products. One report has appeared in 1983, using polymer-bound triphenylphosphine for the formation of esters via the Mitsunobu reaction.¹⁴

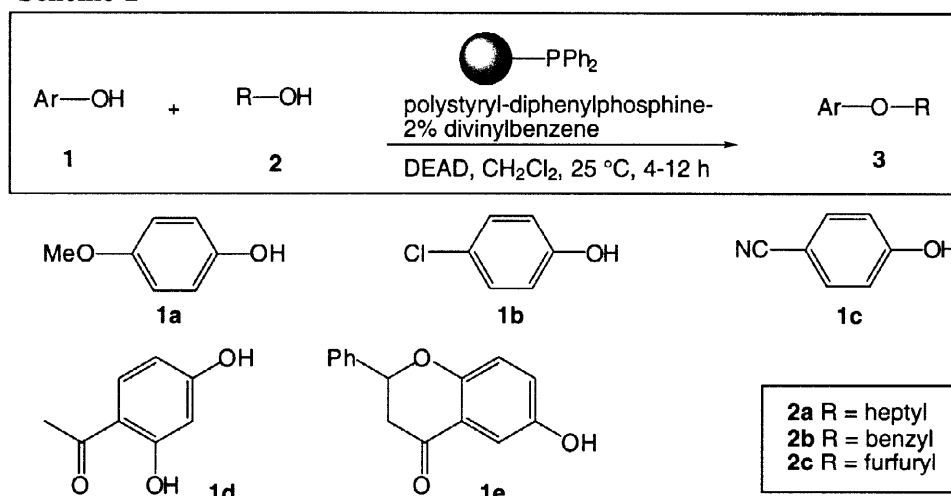
We are now detailing the first example of a Mitsunobu reaction using commercially available polymer-bound triphenylphosphine¹⁵ in the reaction between phenols and alcohols to form aryl ethers (Scheme 1). In this approach the polymer-bound phosphines are easily removed by filtration.

Scheme 1



We have prepared a 15-membered aryl ether library from five commercially available phenols (Aldrich) with electron withdrawing and electron releasing groups and three representative alcohols (Scheme 2 and Tables 1-3). In a typical experiment, polymer-bound triphenylphosphine (1.5 equiv, 3 mmol p/g resin),¹⁵ DEAD (1.5 equiv), the alcohol (1.5 equiv), and the phenol (1 equiv) in CH₂Cl₂ were stirred under an argon atmosphere at room temperature for 4-12 hours. The resin was filtered off and washed thoroughly with dichloromethane. The solvent was removed under reduced pressure and the crude product was purified by short path silica gel column chromatography filtration (the yields in the Tables refer to isolated yields, obtained after purification). In some cases (Table 1, entries 4, 5, 7, 8) the organic layer was first washed with KOH solution (5%), followed by an HCl-wash (5%) to remove unreacted phenol. All aryl ethers thus obtained were characterized by ¹H NMR, ¹³C NMR, and MS spectrometry. Spectral data for compound **3m** are given as a representative example.¹⁶

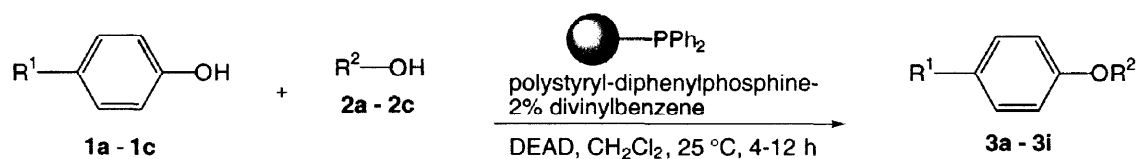
Scheme 2



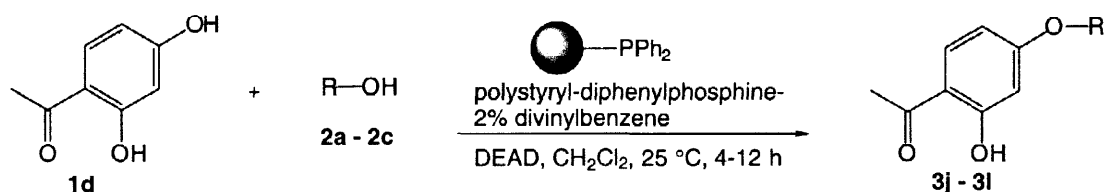
The reaction was first carried out with three 4-phenyl substituted phenols **1a-1c** (entries 1-9 in Table 1). Electron withdrawing substituents at the aromatic ring (Cl and CN) accelerated the rate of reaction (entries 4 - 8 in Table 1), whereas the presence of an electron donating substituent (OMe) generally reduced the reaction rate, resulting in a longer time for the completion of the reaction (entries 1 - 3 in Table 1). Reactions with 2,4-dihydroxyacetophenone yielded monoalkylated products in good yields (entries 1-3 in Table 2) due to the existence of a H-bond between the 2-hydroxyl group and the ketone. The Mitsunobu chemistry was also extended to the synthesis of flavanone ethers (Table 3, entries 1-3).

The relatively low yields in the reactions of the phenols with furfuryl alcohol (entries 3, 6, and 9 in Table 1, entries 3 in Tables 2 and 3) may be a result of the tendency of furfuryl alcohol to polymerize in the presence of acids or may be due to its air sensitivity.

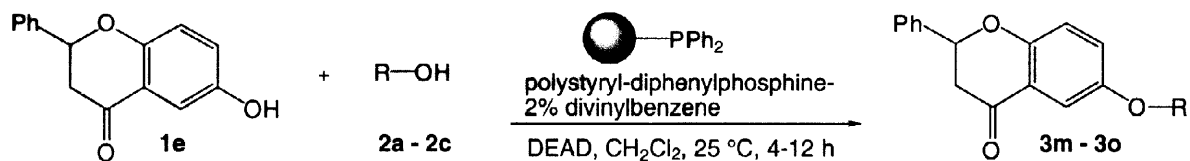
In summary, we have demonstrated the utility of polymer-bound triphenylphosphine as a traceless reagent for aryl ether synthesis using Mitsunobu conditions. An aryl ether combinatorial library was prepared from readily available phenols and alcohols. The use of polymer-supported triphenylphosphine should expand the versatility of the Mitsunobu reaction in the preparation of solution-phase combinatorial libraries.

Table 1. Reactions of 4-substituted phenols **1a-1c** with alcohols **2a-2c** in the Mitsunobu reaction

Entry	Phenol	Alcohol	Product	Yield (%)	Reaction Time (h)	mp (°C)
1	1a	2a	3a R ¹ = OMe R ² = heptyl	78	5	40
2	1a	2b	3b R ¹ = OMe R ² = benzyl	86	6	65
3	1a	2c	3c R ¹ = OMe R ² = furfuryl	63	5	60
4	1b	2a	3d R ¹ = Cl R ² = heptyl	84	4	oil
5	1b	2b	3e R ¹ = Cl R ² = benzyl	88	4	70
6	1b	2c	3f R ¹ = Cl R ² = furfuryl	65	4	oil
7	1c	2a	3g R ¹ = CN R ² = heptyl	88	4	oil
8	1c	2b	3h R ¹ = CN R ² = benzyl	94	4	62
9	1c	2c	3i R ¹ = CN R ² = furfuryl	68	12	oil

Table 2. Reactions of 2,4-dihydroxyacetophenone (**1d**) with alcohols **2a-2c** in the Mitsunobu reaction

Entry	Phenol	Alcohol	Product	Yield (%)	Reaction Time (h)	mp (°C)
1	1d	2a	3j R = heptyl	72	5	oil
2	1d	2b	3k R = benzyl	81	4	96
3	1d	2c	3l R = furfuryl	69	12	oil

Table 3. Reactions of 6-hydroxyflavanone (**1e**) with alcohols **2a - 2c** in the Mitsunobu reaction

Entry	Phenol	Alcohol	Product	Yield (%)	Reaction Time (h)	mp (°C)
1	1e	2a	3m R = heptyl	76	5	69
2	1e	2b	3n R = benzyl	85	4	95-98
3	1e	2c	3o R = furfuryl	59	12	78

Acknowledgments: We gratefully acknowledge financial support from the National Cancer Institute (N01-CM-67259), Kansas Technology Enterprise, and the University of Kansas.

References and Notes:

- For review: Bunin, B. A. *The Combinatorial Index*; Academic: San Diego, 1998.
- For review: Wilson, S. R.; Czarnik, A. W. *Combinatorial Chemistry: Synthesis and Application*; Wilson, S. R.; Czarnik, A. W., Ed.; Wiley: New York, 1997.
- For review: Mitscher, L. A. *Chemtracts-Org. Chem.* **1995**, 8, 19.
- For review: Fecik, R. A.; Frank, K. E.; Gentry, E. J.; Menon, S. R.; Mitscher, L. A.; Telikapali, H. *Med. Res. Rev.* **1998**, 3, 149.
- For review: Thompson, A. A.; Ellman, J. A. *Chem. Rev.* **1996**, 96, 555.
- For review: Hermkens, P. H. H.; Ottenheim, H. C. J.; Rees, D. *Tetrahedron* **1996**, 53, 5643.
- For example: Cheng, S.; Comer, D. D.; Williams, J. P.; Meyers, P.L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, 118, 2567.
- For review: Merritt, A. T. *Combi. Chem. High Through. Screen.* **1998**, 1, 57.
- For example: Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, 119, 7632.
- For example: Parlow, J. J.; Naing, W.; South, M. S.; Flynn, D. L. *Tetrahedron Lett.* **1997**, 38, 7959.
- For review: Mitsunobu, O. *Synthesis* **1981**, 1.
- For review: Hughes, D. L. *Org. React.* **1992**, 42, 335.
- For review: Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, 28, 127.
- Amos, R. A.; Emblidge, R. W.; Havens, N. J. *Org. Chem.* **1983**, 48, 3598.
- The polymer-bound triphenylphosphine (~ 3 mmol triphenylphosphine/g resin) was obtained from Fluka (catalogue no. 93093). Polystyrene is crosslinked with 2% divinylbenzene, diphenylphosphinated.
- Data for compound **3m**: ¹H NMR (400 MHz CDCl₃) δ 0.92 (m, 3 H), 1.34-1.47 (m, 8 H), 1.80 (m, 2 H), 2.90 (dd, *J* = 2.9, 17 Hz, 1 H), 3.09 (dd, *J* = 13, 17 Hz, 1 H), 3.98 (t, *J* = 6.5 Hz, 2 H), 5.46 (dd, *J* = 2.8, 13 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 1 H), 7.13 (m, 1 H), 7.36-7.51 (m, 6 H); ¹³C NMR (100.6 MHz, CDCl₃) δ 14.5, 23.0, 26.3, 29.4, 29.6, 32.1, 45.0, 69.0, 80.0, 108.6, 119.7, 121.1, 126.1, 126.5, 126.7, 129.1, 129.2, 139.3, 154.2, 156.5, 192.4; mp 69 °C.