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Diphenyl 2-Pyridylphosphine and Di-*tert*-butyl Azodicarboxylate:Convenient Reagents for the Mitsunobu Reaction

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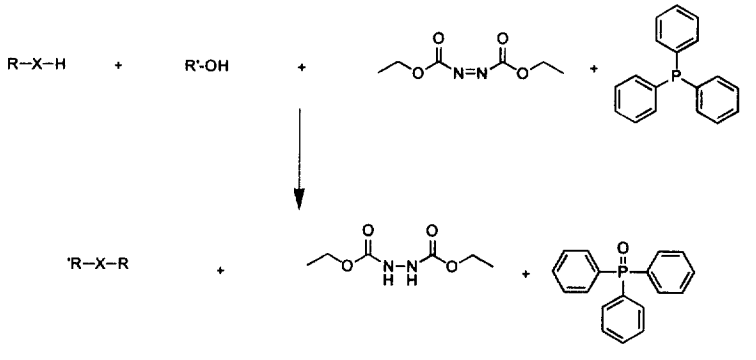
Abstract: New reagents that resolve the problem of separating products from the numerous byproducts in the Mitsunobu reaction have been introduced. Substitution of a basic triarylphosphine and an acid labile azodicarboxylate for triphenylphosphine and diethy azodicarboxylate provide an improved procedure allowing for facile isolation of desired products in good yields and excellent purity.

Keywords: *Mitsunobu reactions*

The Mitsunobu reaction, provides an extremely useful and versatile synthetic method for a large array of products.[1] However, the use of this method is complicated by the resulting complex reaction mixtures containing product, triphenylphosphine oxide and the reduced azodicarboxylate, as well as unreacted starting material (Scheme 1). Diethyl ether precipitation can remove some of the byproducts and assist in purification of products, but extensive chromatography is often required to separate the desired material from the large mass of byproducts. We sought a method, which would give the same flexibility and high yields, but would avoid the complex reaction mixtures and hence tedious purification.

Scheme 1.



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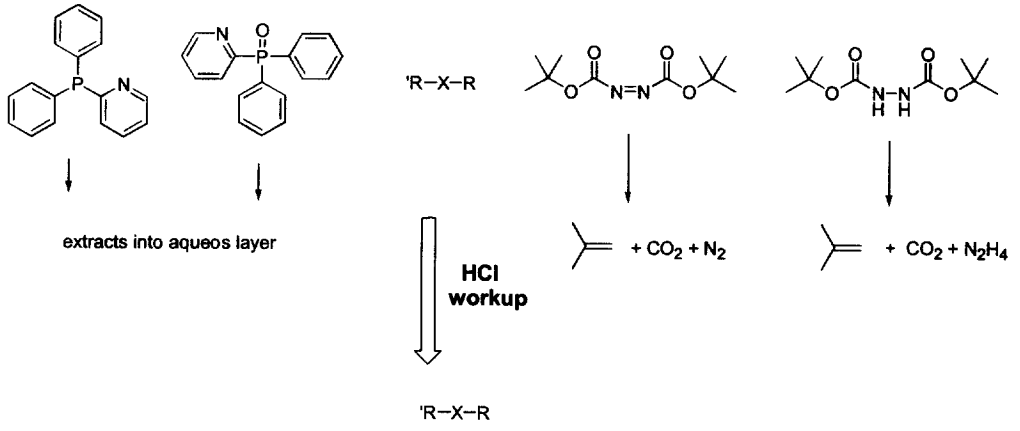
We report an improved procedure for the Mitsunobu coupling reaction that uses the readily available reagents diphenyl-2-pyridylphosphine[2,3] and di-*tert*-butylazodicarboxylate [3]. As shown in Scheme 2, the reagents themselves and their respective oxidation or reduction products, are either directly soluble in aqueous acid or are converted to gaseous byproducts and water soluble materials on treatment with acid. Initially we attempted to introduce a basic group on to an azodicarboxylate side chain to render it acid soluble, but this proved to be difficult and unrewarding. However, we discovered that commercially available t-butyl azodicarboxylate, when treated with mineral acids, readily decomposed to carbon dioxide and nitrogen. Similarly, the reduced form yielded gaseous byproducts and hydrazine which are readily removed with an acid extractive workup. Thus by the combined use of the above two reagents, purification of reaction products was easily achieved.

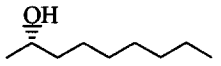
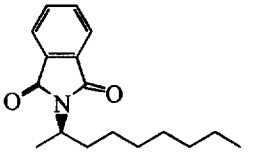
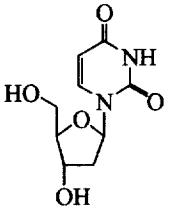
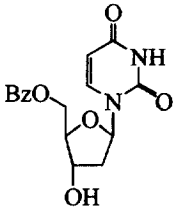
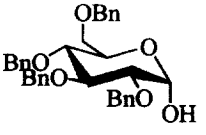
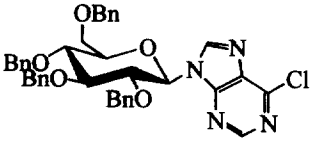
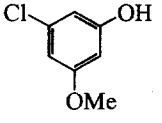
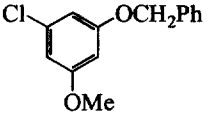
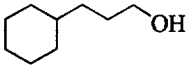
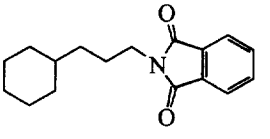
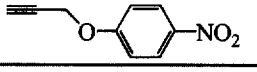
Scheme 2.



The reaction conditions are suitable for an extensive range of substrates giving moderate to good yields and excellent purities of the crude product (see Table 1). The reactions are typically run overnight and worked up by adding 4M HCl in dioxane followed by an aqueous acid wash. The HCl in dioxane is necessary to ensure complete decomposition of the azodicarboxylate products.

A typical experimental procedure is: A mixture of 3-chloro-5-methoxyphenol (79 mg, 0.5 mmol), diphenyl-2-pyridylphosphine (197 mg, 0.75 mmol) and benzyl alcohol (54 mg, 0.5 mmol) was dissolved in anhydrous tetrahyrofuran under an atmosphere of nitrogen. To this solution was added di-*tert*-butylazodicarboxylate (172 mg, 0.75 mmol) in one portion and the resulting mixture was stirred at room temperature for one day. A gas chromatogram/mass spectrum of an aliquot showed complete conversion of starting material to the desired product after 24 hours. A solution of hydrogen chloride in dioxane (2 mL, 4 M) was added to

Table1. Mitsunobu Reaction with diphenyl-2-pyridylphosphine and di-*tert*-butylazodicarboxylate

Entry	Substrate	Product	Yield
1			56%
2			57%
3			30%
4			69%
5			52%
6			68%

the mixture and after stirring for one hour the excess solvent was evaporated. The residue was dissolved in ether or dichloromethane and shaken vigorously with 4 M aqueous hydrochloric acid twice. The organic layer was dried with anhydrous magnesium sulfate and the solvent evaporated. Flash column chromatography (20% ethyl acetate in hexanes) gave the desired benzyl ether as a pale yellow oil (86 mg, 69%). All products were analyzed by NMR and mass spectroscopy and the spectra compared, when available, to those of authentic samples.[4]

In most cases the material isolated after the acid treatments was pure and did not require any further manipulation. However, reported yields are those obtained after a final filtration through a short path silica gel column. The generality and utility of this new version of the

Mitsunobu reaction is evident from the examples in Table 1. It should be noted that products with basic groups may be difficult to purify with this new method. However the procedure is convenient even in the case of the highly functionalized substrates (reaction 3) where the product was easily isolated in moderate yield. For the sake of comparison, reactions 3 and 4 were repeated, using the usual Mitsunobu reagents. Under equal conditions of concentration and scale as those reported in Table 1, the benzyl ether in reaction 4 was isolated in similar yield (65%) using triphenylphosphine and DEAD, while the coupling product of example 4 was produced in greater yield but as a mixture of N-9 and N-7 adducts (1.7: 1.0 ratio).

Thus, the Mitsunobu coupling procedure was found to proceed in good yields using diphenyl-2-pyridylphosphine and di-*tert*-butyl azodicarboxylate. An acid workup removed byproducts from the reaction mixture to give crude products of excellent purities. This modified procedure will have applications to solution phase combinatorial chemistry[5], where removal of reagents is often a limiting factor, as well as large scale process chemistry.[6]

References and Notes

1) The Mitsunobou reaction has been extensively reviewed, see: Mitsunobu, O. *Synthesis* **1981**, 1. Simon, C; Sandor H.; Sandor, M., *J. Heterocycl. Chem.*, **1997**, *34*, 349. Hughes, D. L. *Org. Reactions*, **1992**, *42*, 335.
2) Two reports of the use of pyridyl diphenylphosphine and dimethylamino-triphenylphosphine in conjunction with diethyl azodicarboxylate have appeared. However these papers did not attempt to address the problems associated with the azodicarboxylate and its reduced form. Camp, D.; Jenkins, I. D. *Aust. J. Chem.* **1988**, *41*, 1835. Von Izstein, M.; Mocerino, M. *Synth. Commun.*, **1990**, *20*, 2049.
3) Available from Aldrich Chemical Co., Milwaukee, WI.
4) Spectral data for new compounds:
Entry 4: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.44 (m, 5H); 6.60 (dd, J = 2.1, 1.8 Hz, 1 H); 6.53 (dd, J = 2.4, 1.8 Hz, 1 H); 6.42 (dd, J = 2.4, 2.1 Hz, 1 H); 5.02 (s, 2 H); 3.76 (s, 3 H). MS (EI) *m/e*: 248 (M^+).
Entry 3: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.67 (s, 1H); 8.03 (s, 1H); 6.61-7.37 (m, 20H); 5.57 (d, J = 8.7 Hz, 1H), 4.99 (d, J = 10.8 Hz, 1H); 4.94 (d, J = 10.8 Hz, 1H); 4.88 (d, J = 9.9 Hz, 1H); 4.64 (d, J = 9.9 Hz, 1H); 4.62 (d, J = 11.7 Hz, 1H), 4.55 (d, J = 12.4 Hz, 1H); 4.48 (d, J = 12.4 Hz, 1H); 4.17 (d, J = 11.7 Hz, 1H); 4.07 (dd, J = 9.3, 9.0 Hz, 1H); 3.84-3.94 (m, 2H), 3.67-3.78 (m, 3H). CI MS *m/e*: 677 ($[M+H]^+$).
5) For a recent example of the application of Mitsunobu reaction to solid phase combinatorial chemistry see: Tunoori, A. R.; Dutta, D.; Georg, G. I. *Tetrahedron Lett.*, **1998**, *39*, 8751.
6) Examples of parallel solution phase synthesis using liquid extraction are: Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L. and Boger, D. L. *J. Am. Chem. Soc.* **1996**, 118(11) 2567. Whitten, J. P.; Xie, Y. F.; Erickson, P. E.; Webb, T. R.; De Souza E. B.; Grigoriadis, D. E.; and McCarthy, J. R. *J. Med. Chem.* **1996**, 39(22).