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Use of Sonication for the Coupling of Sterically Hindered Substrates in the Phenolic Mitsunobu Reaction

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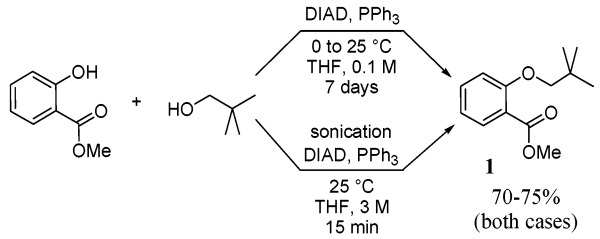
Abstract: A vast rate increase in the Mitsunobu reaction of phenols with alcohols where either or both are sterically hindered has been achieved by the use of high concentration combined with sonication.

The Mitsunobu reaction is extensively used in organic synthesis for the preparation of alkyl aryl ethers under mild conditions.[1] The method has proven successful in the coupling of a wide variety of phenol and alcohol substrates and has been optimized for use in the solid phase.[2] However, the reaction is prohibitively slow in the case of sterically hindered substrates.[3] For example, when we attempted the Mitsunobu reaction of methyl salicylate with neopentyl alcohol to obtain compound **1**, a reaction time of 7 days was required to achieve synthetically useful yields (70−75%). However, when the reaction concentration was increased from 0.1 to 3.0 M and submitted to sonication conditions, compound **1** was obtained in 75% yield *in only 15 min*. In this report, we demonstrate the utility of this variation of the Mitsunobu reaction in the synthesis of a variety of hindered aryl alkyl ethers.



In our initial attempts to reduce reaction times in the methyl salicylate/neopentyl alcohol coupling reaction, several reported variations to the original Mitsunobu reaction were examined. These included solvent (THF, DMF, benzene, and dioxane), temperature, and various phosphines.[4] We observed that rate of the coupling reaction was only moderately solvent dependent with a slight preference for THF relative to the other solvents tested. An increase in reaction temperature (to 40 and 55 °C) did enhance the rate of the coupling reaction giving 40−50% yields after 72 h. However, the warmed reactions were accompanied by increased side product formation. Electron-deficient phosphines such as (*m*-chlorophenyl)$_3$P, (*p*-fluorophenyl)$_3$P, and $(F_5C_6)_3P$ exhibited no improvement over triphenylphosphine. In the case of tri-*n*-butylphosphine, no coupling product was obtained.

We also attempted to enhance the rate of the coupling reaction by increasing the concentration. To achieve efficient stirring, we found that the reaction concentration could not exceed 0.5 M (with respect to the phenol substrate). More concentrated reaction mixtures were simply too viscous for stirring with magnetic or mechanical stirring equipment. Thus we initially turned our attention to sonication[5] as a means to achieve more efficient mixing at higher reaction concentrations. At a reaction concentration of 1.0 M combined with sonication, the Mitsunobu reaction of methyl salicylate and neopentyl alcohol gave coupling product **1** in 69% yield in 12 h. When the concentration was further increased to 3.0 M and submitted to sonication, coupling product **1** was obtained in 75% yield in 15 min. Further sonication did not lead to increased yields.

To define the scope and limitations of this new modification of the Mitsunobu reaction, a variety of phenols and alcohols of varying degrees of steric congestion were investigated. Thus mono- and di-*o*-substituted phenols were reacted with cyclohexanol and neopentyl alcohol (Table 1). As expected, coupling reactions involving cyclohexanol at typical reaction concentrations (0.1 M with respect to the phenol) were sluggish. In all cases, high concentration combined with sonication resulted in higher yields in 15 min than was observed with standard Mitsunobu conditions over a 24-h period. Of particular note is the coupling of methyl salicylate and cyclohexanol (entry 5) yielding 85% of the coupling product under sonication conditions. Over 5 days of reaction time was required to achieve similar yields with standard conditions (results not shown).

The utility of the sonication approach is further highlighted in the reaction of sterically hindered phenols with neopentyl alcohol. Due to their high degree of steric hindrance, neopentyl substrates generally undergo rearrangements and eliminations as electrophiles in S_N2-type reactions leading to significant side-product formation.[6] We have observed that Mitsunobu reactions involving neopentyl alcohols lead to minimal side product formation. However, under standard conditions, these coupling reactions are prohibitively slow. For example, the coupling reaction of neopentyl alcohol and *o*-*tert*-butyl phenol (Entry 7) gave only a trace amount of product after 24 h

(1) Mitsunobu, O. *Synthesis* **1981**, 1.

(2) (a) Richter, L. S.; Gadek, T. R. *Tetrahedron Lett.* **1994**, *35*, 4705. (b) Lizarzaburu, M. E.; Shuttleworth, S. J. *Tetrahedron Lett.* **2002**, *43*, 2157.

(3) For other examples of prohibitively slow Mitsunobu coupling reactions see: (a) Marchand, A. P.; Dave, P. R. *J. Org. Chem.* **1988**, *53*, 1212. (b) Marchand, A. P.; Dave, P. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 124. (c) Marchand, A. P.; Dave, P. R. *Tetrahedron Lett.* **1989**, *30*, 2297.

(4) Camp, D.; Jenkins, I. D. *Aust. J. Chem.* **1992**, *45*, 47.

(5) The sonication reactions described involve the partial submersion of the reaction vessel into an ultrasonication bath at room temperature. The model used in this study was a Mettler Electronics model 4.6 (40 kHz).

(6) Although recent modifications to the Williamson ether synthesis reaction have led to improved results: (a) Masada, H.; Gotoh, H.; Ohkubo, M. *Chem. Lett.* **1991**, *10*, 1739. (b) Masada, H.; Yammamoto, T.; Yamamoto, F. *Nippon Kagaku Kaishi* **1995**, *12*, 1028.

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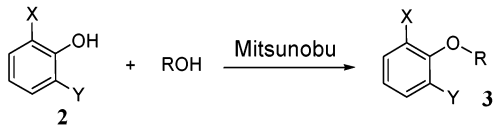
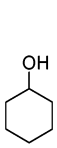
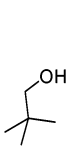
TABLE 1. Comparison of Sonication versus Standard Conditions for the Mitsunobu Reaction of Sterically Hindered Phenols with Neopentyl Alcohol and Cyclohexanol



Entry	ROH	X	Y	% Isolated Yield of 3[a] Sonication[b]	Std. Cond.[c]
1		CH_3	H	61	41
2		t-Bu	H	60	32
3		CF_3	H	66	47
4		CH_3	CH_3	51	32
5		CH_3OCO	H	85	16
6		CH_3	H	49	<2
7		t-Bu	H	39	<2
8		CF_3	H	58	8
9		CH_3	CH_3	42	12
10		CH_3OCO	H	75	11

[a] All yields shown are for products obtained pure with silica gel flash chromatography. [b] See Experimental Section for a representative procedure. [c] Same stoichiometry as sonication conditions except 0.1 M in solvent and slow addition of DIAD to the reaction mixture at 0 °C with warming to room temperature. Reported yields are after 24 h.

at typical reaction concentrations. With the use of high concentration and sonication, *o*-*tert*-butyl phenol was coupled to neopentyl alcohol in 39% isolated yield after 15 min of reaction. Similar rate enhancements were seen in the coupling of neopentyl alcohol with *o*-methyl and *o*-trifluoromethyl phenol (Entries 6 and 8), 2,6-dimethylphenol (Entry 9), and methyl salicylate (Entry 10). As in the case of the Mitsunobu reaction of methyl salicylate and neopentyl alcohol described above, increasing the sonication time for the reactions reported in Table 1 did not lead to discernible improvement in yields. The sonication reactions seemed to have reached their ultimate yields in 10 to 15 min.

Our modification to the Mitsunobu reaction has been successfully applied to coupling reactions ranging from the milligram to near-gram scales. However, due to the explosive hazards of azodicarboxylates, we do not recommend that the sonication procedure described in this report be used for reaction scales larger than 2 g unless precautions are taken to remove excessive heat buildup during the reaction.

While the mechanism for the Mitsunobu reaction has been studied in detail by numerous investigators,[7] the reasons for the dramatic increase in reaction rate that results from high concentration and sonication are not entirely clear. The rate acceleration effect observed with our protocol may simply be based on the high concentration with the sonic waves providing efficient mixing of the highly viscous reaction mixture and generating localized hot spots.[8] However, the cavitation effects of sonication have also been attributed to the generation of coordinatively unsaturated species or free radicals[9] leading to the identification of sonochemically enhanced radical pathways in a variety of well-known reactions.[10] Since radical intermediates have been observed in the Mitsunobu reaction,[11] the observed rate increase resulting from sonication may be, in part, the result of an enhancement of a radical reaction pathway. Studies to investigate the origin of the rate enhancement in the Mitsunobu reaction are currently underway.

In summary, the Mitsunobu coupling reaction of sterically hindered phenols and alcohols is greatly accelerated by the use of high reaction concentrations in combination with sonication.

Experimental Section

Representative Experimental Procedure. To a round-bottomed flask was added 2,6-dimethylphenol (500 mg, 4.10 mmol), neopentyl alcohol (378 mg, 4.30 mmol), triphenylphosphine (1.13 g, 4.30 mmol), and THF (1.4 mL). The reaction vessel was then lowered into a 40-kHz sonication bath (Mettler Electronics model 4.6) and sonicated for several minutes (to allow for mixing) giving a clear and highly viscous solution. While sonicating, diisopropylazodicarboxylate (0.854 mL, 4.30 mmol) was added dropwise to the reaction mixture over the course of 2 min. Overall, the reaction mixture (amber color) was sonicated for 15 min. The reaction mixture was triturated with a minimal amount of cold hexanes (3 mL) to remove the majority of the triphenylphosphine oxide byproduct. The hexane mixture was then purified by flash chromatography (silica gel, 3% EtOAc in hexanes) to give 2,6-dimethylphenyl neopentyl ether (Table 1, Entry 9) (331 mg, 42%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, J = 7.5 Hz, 2H), 6.92 (m, 1H), 3.42 (s, 2H), 2.29 (s, 6H), 1.11 (s, 9H). HRMS calcd for $C_{13}H_{20}O$ 192.1515, found 192.1506.

The following aryl ethers from Table 1 have been reported in the literature: Entry 1,[12] Entry 4,[13] Entry 5,[14] Entry 6,[15] and Entry 7.[16] Characterization data for new compounds are given below.

2-(*tert*-Butyl)phenyl cyclohexyl ether (Table 1, Entry 2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 7.0 Hz, 1H), 7.14 (d,

(7) The following references describe studies of the Mitsunobu reaction mechanism: (a) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751 (also see corrections: *J. Org. Chem.* **2003**, *68*, 1176). (b) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045. (c) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487.

(8) Suslick, K. S.; Hammerton, D. A.; Cline, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 5641.

(9) Luche, J. L.; Einhorn, C.; Einhorn, J. *Tetrahedron Lett.* **1990**, *31*, 4125.

(10) A number of investigations have identified the origin of sonochemical rate enhancement in reactions such as the following: (a) Diels−Alder: Caulier, T. P.; Reisse, J. *J. Org. Chem.* **1996**, *61*, 2547. (b) Barbier: Souza-Barboza, J. C.; Pétrier, C.; Luche, J. L. *J. Org. Chem.* **1988**, *53*, 1212. (c) Epoxide reductions: Moreno, M. J. S.; Melo, M. L.; Neves, A. S. C. *Tetrahedron Lett.* **1993**, *34*, 353.

(11) (a) Camp, D.; Hanson, G. R.; Jenkins, I. D. *J. Org. Chem.* **1995**, *60*, 2977. (b) Eberson L.; Persson, O.; Svensson, J. O. *Acta Chem. Scand.* **1998**, *52*, 1293.

(12) Abdurasuleva, A. R.; Israilova, Sh. A. *Zh. Obshch. Khim.* **1962**, *32*, 704.

(13) Pauson, P. L.; Dalgleish, D. T.; Nonhebel, D. C. *J. Chem. Soc. Sect. C* (*Organic*) **1971**, *6*, 1174.

(14) Eisner, A.; Perlstein, T.; Ault, W. C. *J. Am. Oil Chem. Soc.* **1963**, *40* (10), 594.

(15) Seyden-Penne, J.; Habert-Somny, A.; Cohen, A. M. *Bull. Soc. Chim. France* **1965**, *3*, 700.

(16) Masada, H.; Yammamoto, T.; Yamamoto, F. *Nippon Kagaku Kaishi* **1995**, *12*, 1028.

J = 7.0 Hz, 2.0 Hz, 1H), 6.84 (m, 2H), 4.38 (m, 1H), 2.02 (m, 2H), 1.82 (m, 2H), 1.63 (m, 4H), 1.47 (m, 2H), 1.40 (s, 9H). HRMS calcd for $C_{16}H_{24}O$ 232.1827, found 232.1836.

2-Trifluoromethylphenyl cyclohexyl ether (Table 1, Entry 3): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 1H), 7.44 (m, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.94 (m, 1H), 4.42 (m, 1H), 1.90 (m, 2H), 1.81 (m, 2H), 1.68 (m, 2H), 1.39 (m, 4H). HRMS calcd for $C_{13}H_{15}F_3O$ 244.1075, found 244.1063.

2-Trifluoromethylphenyl neopentyl ether (Table 1, Entry 8): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 1H), 7.46 (m, 1H), 6.97 (m, 2H), 3.66 (s, 2H), 1.07 (s, 9H). HRMS calcd for $C_{12}H_{15}F_3O$ 232.1075, found 232.1071.

2-(Methoxycarbonyl)phenyl neopentyl ether (Table 1, Entry 10): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 7.5 Hz, 1H), 7.42 (m, 1H), 6.93 (m, 2H), 3.90 (s, 3H), 3.66 (s, 2H), 1.07 (s, 9H). HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1251.

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Supporting Information Available: ^{1}H NMR spectra for compounds given in Entries 2, 3, 8, 9, and 10 of Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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