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# EFFICACIOUS MODIFICATION OF THE MITSUNOBU REACTION FOR INVERSIONS OF STERICALLY HINDERED SECONDARY ALCOHOLS

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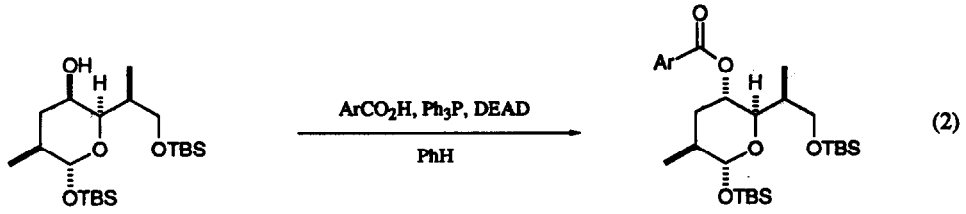
**Abstract.** A practical modification of the Mitsunobu protocol for effecting stereochemical inversions of alcohols has been discovered in which use of *p*-nitrobenzoic acid as the nucleophilic partner results in significantly improved yields with relatively hindered substrates.

The Mitsunobu reaction has been widely utilized for the refunctionalization of alcohols.[2] In particular, it is an important synthetic tool for inverting alcohol stereochemistry under mild, essentially neutral, reaction conditions according to eq 1. While the efficacy of this procedure is well documented for a variety of substrates,[2] the reaction has proven inherently sensitive to the steric environment of the alcohol.[3] Specifically, primary alcohols react in preference to more sterically encumbered secondary substrates. While such selectivity can obviously be used to advantage, Mitsunobu inversions of hindered alcohols has proven problematic[4] typically resulting in low yields or returned starting material. Herein we report a simple modification of this reaction that results in substantially improved yields for the inversion of sterically hindered secondary alcohols.


(1)

A key transformation in our synthetic approach toward the ansamycin antibiotic macbecin[5] required inversion of the secondary alcohol moiety of **1** (eq. 2). Surprisingly, subjection of **1** to standard Mitsunobu reaction conditions[2] [$PhCO_2H$, $Ph_3P$, diethylazodicarboxylate, 25 °C] in THF returned only starting material. Zbiral[6] reported employing benzene rather than THF as a medium for the Mitsunobu reaction gave higher yields of inverted

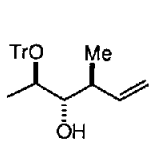



(2)

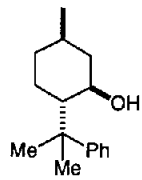
**1** **2**

product for several steroid-derived substrates. Indeed, use of benzene as a solvent in the present instance led to the formation of the desired product **2** (Ar = Ph), albeit in only 27% yield. During the course of surveying a variety of modifications of the Mitsunobu reaction, we discovered that mere replacement of benzoic acid with *p*-nitrobenzoic acid[7] resulted in dramatically improved yields in the inversion process. Thus, when **1** was subjected to these modified conditions, **2** (Ar = *p*-$O_2NC_6H_4$-) was obtained in 86% yield, which represents a greater than three-fold increase in efficiency relative to the use of benzoic acid as the nucleophile.

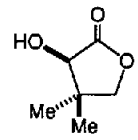
In order to define the scope and limitations of this new modification of the Mitsunobu reaction, secondary alcohols of varying degrees of steric congestion were systematically investigated. Examination of the results summarized in the Table[8] reveal that these conditions are particularly effective for secondary alcohols with substitution on the α-carbon (entries 1 - 6), and in most cases dramatically improved yields of inverted product were observed.[9] However, extension of the methodology to more sterically congested alcohols often resulted in diminished reactivity and low yields. For example, substrates such as **3**, in which the alcohol moiety is flanked by two substituents, gave none of the desired product, even under forcing reaction conditions (excess reagent, prolonged reaction times, and/or heating). Little or no reactivity was also observed for alcohols with relatively large α-substituents (*e.g.*, **4** - **6**). In contrast, secondary alcohols lacking an α-substituent, such as dihydro-*epi*-cholesterol (entry 7), exhibited essentially identical reactivity when either acidic component was employed. Interestingly, use of aromatic carboxylic acids with electron releasing rather than electron withdrawing substituents, such as is exemplified in the case of *p*-methoxybenzoic acid (entry 2), resulted in poor yields of hydroxyl inversion. The use of *p*-nitrobenzoic acid as the nucleophile in Mitsunobu inversions offers two other potential advantages: (1) the *p*-nitrobenzoate esters are more readily deprotected via saponification than the corresponding benzoates; and (2) the *p*-nitrobenzoate esters are often crystalline and may be easily purified.[10]



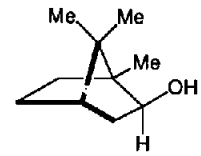

**3**




**4**



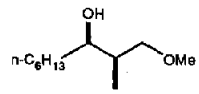
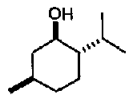
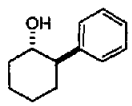
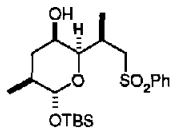
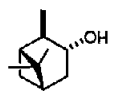
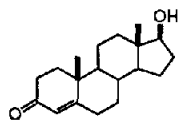
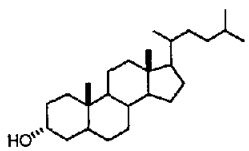

**5**




**6**

While the general mechanistic features of the Mitsunobu process have been well documented,[11] the reasons for the dramatic increase in yields that result when using *p*-nitrobenzoic acid to effect inversions for sterically hindered alcohols is not entirely clear. Recent mechanistic work by both Hughes[11f] and Jenkins[11h] has indicated the $pK_a$ of the acid has a profound effect on the reaction pathway. Specifically, Jenkins[11h] has shown via $^{31}$P-NMR that employing acids possessing lower $pK_a$'s than benzoic acid (such as trifluoroacetic acid and *p*-nitrobenzoic acid) results in equilibria favoring formation of the requisite activated oxyphosphonium intermediate that undergoes the inversion process. In addition, carboxylate basicity has been shown to play an integral role in defining the partitioning of the various reactive intermediates in the Mitsunobu reaction.[11f] A study of the mechanistic intricacies in order to provide some insights regarding the role that *p*-nitrobenzoic acid plays to improve the efficiency of the Mitsunobu reaction in sterically encumbered systems is the subject of current investigation and will be reported in due course.

**Table. Mitsunobu Inversions of Secondary Alcohols Using Aryl Carboxylic Acids.**

| *entry* | *alcohol* | *$ArCO_2H$* | *Conditions*[a] | *Yield (%)* |
|---|---|---|---|---|
| 1 |  | *p*-$O_2NC_6H_4CO_2H$<br>$PhCO_2H$ | 7.0 equiv; RT, 17 h | 73<br>19 |
| 2 |  | *p*-$O_2NC_6H_4CO_2H$<br>$PhCO_2H$<br>*p*-$MeOC_6H_4CO_2H$ | 1.2 equiv., RT, 1 h | 84<br>27<br>17 |
| 3 |  | *p*-$O_2NC_6H_4CO_2H$<br>$PhCO_2H$ | 1.5 equiv., RT, 6 h | 99<br>58 |
| 4 |  | *p*-$O_2NC_6H_4CO_2H$<br>$PhCO_2H$ | 6.0 equiv., RT, 6 h | 72<br>20 |
| 5 |  | *p*-$O_2NC_6H_4CO_2H$<br>$PhCO_2H$ | 1.2 equiv., RT, 1 h | 50<br>35 |
| 6 |  | *p*-$O_2NC_6H_4CO_2H$<br>$PhCO_2H$ | 1.2 equiv., 81 °C,<br>20 min | 89<br>62 |
| 7 |  | *p*-$O_2NC_6H_4CO_2H$<br>$PhCO_2H$ | 2.5 equiv., RT, 1 h | 70<br>67 |

[a] Number of equiv. refers to the stoichiometry of $Ph_3P$, $ArCO_2H$, DEAD with respect to the substrate (optimized for *p*-nitrobenzoic acid in all cases). All reactions were conducted in benzene as solvent.

In summary, simple modification of standard Mitsunobu conditions by substituting *p*-nitrobenzoic acid for benzoic acid resulted in significantly improved yields for the inversion process for a variety of secondary alcohols with a substituent on the α-carbon.

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4. For examples see (a) Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852. (b) Chu, A.; Mander, L. N. *Tetrahedron Lett.* **1988**, *29*, 2727. (c) Kithara, T.; Kurata, H.; Mori, K. *Tetrahedron* **1988**, *44*, 4339. (d) Labidalle, S.; Min, Z. Y.; Reynet, A.; Moskowitz, H. *Tetrahedron* **1988**, *44*, 1171. (e) Hauser, F. M.; Ellenberger, W. P. *J. Org. Chem.* **1988**, *53*, 1118. (f) Willis, C. L. *Tetrahedron Lett.* **1987**, *28*, 6705. (g) Hoeger, C. A.; Johnston, A.D.; Okamura, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 4690. (h) Martin, S. F.; Davidsen, S. K.; Puckette, T. A. *J. Org. Chem.* **1987**, *52*, 1962. (i) Marco, J. A.; Carda, M. *Tetrahedron* **1987**, *43*, 2523. (j) Bal-Tempe, S.; Bhedi, D. N.; de Souza, N. J.; Rupp, R. H. *Heterocycles* **1987**, 26, 1239. (k) Hoppe, D.; Tarara, G.; Wilckens, M.; Jones, P. G.; Schmidt, D.; Stezowski, J. J. *Angew. Chem. Int Ed. Engl.* **1987**, *26*, 1034. (l) Ladlow, M.; Pattenden, G.; Teague, S. J. *Tetrahedron Lett.* **1986**, *27*, 3279. (m) Trost, B. M.; McDougal, P. G. *J. Org. Chem.* **1984**, *49*, 458. (n) Still, W. C.; Gennari, C.; Noguez, J. A.; Pearson, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 260. (o) Herz, W.; Prasad, J. S.; Mohanraj, S. *J. Org. Chem.* **1983**, *48*, 81. (p) Mitsunobu, O.; Ebina, M.; Ogihara, T. *Chem. Lett.* **1982**, 373.
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7. For other examples of the use of *p*-nitrobenzoic acid as the nucleophilic partner, see: (a) Mitsunobu, O.; Kimura, J.; Fujisawa, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 245. (b) Eaton, P; Jobe, P. G.; Reingold, I. D. *J. Am. Chem. Soc.* **1984**, *106*, 6437. (c) Jarosz, S.; Glodek, J.; Zamojski, A. *Carb. Res.* **1987**, *163*, 289. (d) Simon, C.; Makleit, S. *Heterocycles* **1990**, *31*, 787.
8. Stereochemical assignments were made by comparison of the inverted alcohol (after deprotection) with the starting substrate. All new compounds gave satisfactory $^{1}H$ and $^{13}C$-NMR, IR, and high resolution mass spectral or combustion analysis.
9. ***Representative Experimental Procedure***: To a stirred solution of the alcohol **1** (0.53 g, 1.3 mmol), triphenylphosphine (1.67 g, 6.4 mmol), and *p*-nitrobenzoic acid (0.95 g, 5.7 mmol) in dry benzene (25 mL) at room temperature was added diethylazodicarboxylate dropwise (1.0 mL, 6.4 mmol). After approximately 5 min, the slightly orange solution became homogeneous. The solution was then stirred at room temperature for 6 h, whereupon the volatile components were removed *in vacuo* and the residue purified by flash chromatography (silica gel, 2% $Et_2O$ in hexanes) to give 0.63 g (86%) of **2** (Ar = *p*-$O_2NC_6H_4$-) as a white crystalline solid (m.p. = 97 - 99 °C).
10. Similarly, 3,5-dinitrobenzoic acid has been used in order to obtain crystalline products. For representative examples see: (a) Mori, K.; Otsuku, T.; Oda, M. *Tetrahedron* **1984**, *40*, 2929. (b) Mori, K.; Ikunaka, M. *Tetrahedron* **1984**, *40*, 3471.
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