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MITSUNOBU REACTIONS OF N-ALKYL AND N-ACYL SULFONAMIDES-AN EFFICIENT ROUTE TO PROTECTED AMINES

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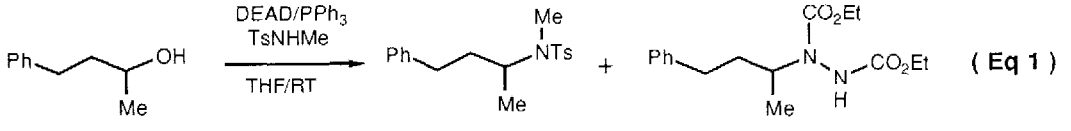
Summary: N-Methyl p-toluenesulfonamide and N-BOC p-toluenesulfonamide can be directly coupled with primary and secondary alcohols under Mitsunobu conditions to afford various sulfonamide-protected amines.

The Mitsunobu reaction is an exceptionally useful and general method in organic synthesis whereby one can replace a hydroxyl group by a wide range of nucleophiles.[1] Both inter- and intramolecular versions of the Mitsunobu reaction have been well documented. A variety of nitrogen nucleophiles have been utilized in this procedure to afford amines and amine derivatives.[1,2] However, to our knowledge sulfonamides have not been described as components of Mitsunobu reactions.[3,4] For some ongoing research projects in these laboratories several different sulfonamide intermediates were required and we considered preparing these compounds directly by a Mitsunobu coupling of a simple aryl sulfonamide and an alcohol.

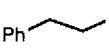
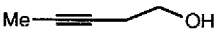
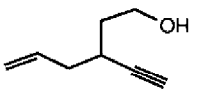
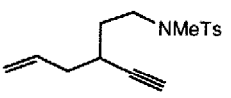
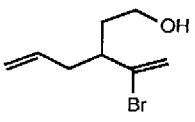
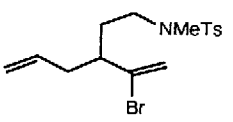
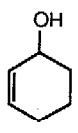
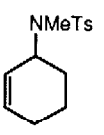
p-Toluenesulfonamide itself is not at all useful in the Mitsunobu reaction since it forms $TsN{=}PPh_3$.[3] However, we found that N-alkyl sulfonamides can in fact be successfully used. For example, treatment of alcohol **1** with N-methyl p-toluenesulfonamide in THF under standard



1 **2** (55%) **3** (18%) **(Eq 1)**

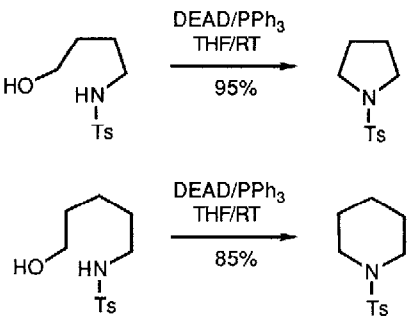
Mitsunobu conditions[1] afforded sulfonamide **2** in moderate yield (**Eq 1**). Examination of the reaction mixture established that DEAD N-alkylation compound **3** was the primary by-product.[5] Additional examples of this coupling are listed in **Table 1** (see experimental procedure below).

Table 1. *Conversion of Alcohols to N-Methyl p-Toluenesulfonamides*

Alcohol	Product	Isolated Yield
		50%
		58%
		51%
		80%
		58%
		62%

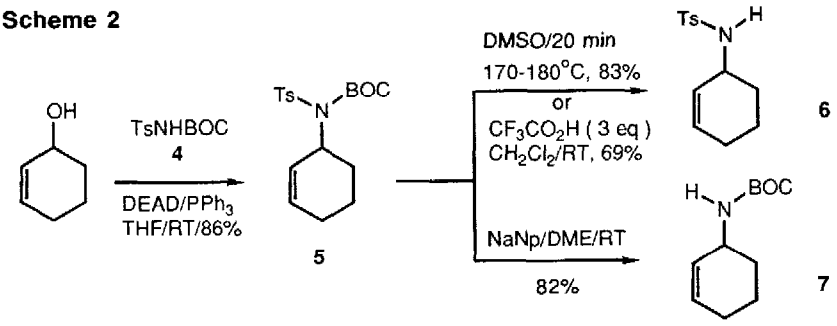
Intramolecular cyclization of sulfonamido alcohols can also be effected (**Scheme 1**). In these cases yields of cycloalkylation products were exceptionally good since the intramolecularity of the process minimizes the competing DEAD alkylation.

Scheme 1



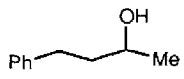
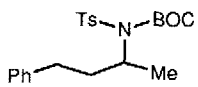
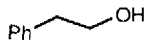
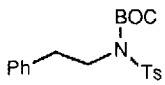
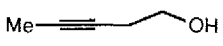
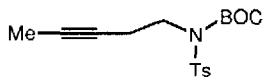
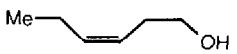
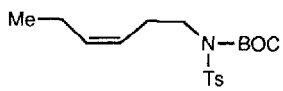
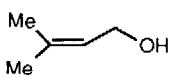
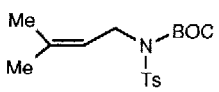
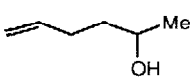
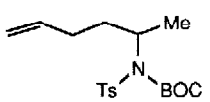
As an alternative to using a primary sulfonamide, we have investigated Mitsunobu reactions of N-acyl sulfonamides. N-BOC p-toluenesulfonamide (4) was prepared in high yield by addition of t-butanol to inexpensive, commercially available tosyl isocyanate (see procedure below).[6] Coupling of 4 with 2-cyclohexen-1-ol gave an 86% yield of N-BOC sulfonamide 5 (**Scheme 2**). Mitsunobu reactions of 4 with various other primary, secondary and allylic alcohols provided the

Scheme 2



corresponding N-BOC p-toluenesulfonamides in excellent yields as shown in **Table 2** (see experimental procedure below).

Table 2. *Conversion of Alcohols to N-BOC p-Toluenesulfonamides*

Alcohol	Product	Isolated Yield
		92%
		97%
		96%
		88%
		85%
		75%

It is possible to selectively remove either of the nitrogen protecting groups of these N-BOC sulfonamides. For example, treatment of 5 with TFA affords sulfonamide **6** (**Scheme 2**). Similarly, thermolysis of 5 in DMSO also provides the deacylated sulfonamide **6**. Alternatively, sodium naphthalenide[7] serves to deprotect 5 to give the N-BOC compound **7**.

We have therefore demonstrated that both N-alkyl and N-acyl sulfonamides are useful nucleophiles in Mitsunobu couplings. In particular, readily available N-BOC p-toluene sulfonamide (4) undergoes high yield Mitsunobu reactions and provides an efficient means of synthesis of protected amines.

Preparation of N-BOC p-Toluenesulfonamide (4). A 100 mL 3-necked flask fitted with a thermometer was charged with 35 mL of t-butanol (freshly distilled from calcium hydride). Freshly distilled p-toluenesulfonyl isocyanate (5.3 mL, 6.9 g, 34.8 mmol) was added to the solution dropwise with stirring over several minutes, causing the reaction temperature to rise to 50-55°C. The reaction mixture was stirred overnight at room temperature. The excess t-butanol was removed under vacuum yielding 9.0 g (94%) of **4** as a white solid, mp 118-120°C, which was sufficiently pure to be used directly in the Mitsunobu reactions. A small sample recrystallized from ethyl acetate/hexane had mp 121-122.5°C (lit[6b] mp 115-117°C): IR (CH_2Cl_2) 3370, 2480, 1600, 1410, 1350, 1150, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.95-7.85 (m, 2H), 7.35-7.30 (m, 2H), 2.44 (s, 3H), 1.38 (s, 9H).

Sulfonamide Mitsunobu Reactions. N-BOC p-toluenesulfonamide (**4**, 88 mg, 0.322 mmol) or N-methyl p-toluenesulfonamide (100 mg, 0.53 mmol) was dissolved in 3 mL of dry THF and triphenylphosphine (168 mg, 0.645 mmol) was added. The solution was stirred under nitrogen and the alcohol (0.215 mmol) was added followed by diethyl azodicarboxylate (0.083 mL, 0.530 mmol). The mixture was stirred at room temperature for 3 h, concentrated in vacuo and the product was purified by flash chromatography on silica gel (4:1 hexanes/ethyl acetate). Isolated yields of products are shown in **Tables 1** and 2.

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References and Notes

1. For a review, see: Mitsunobu, O. Synthesis **1981**, 1.
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5. For recent mechanistic studies on the Mitsunobu reaction, see: (a) Hughes, D.L.; Reamer, R.A.; Bergan, J.J.; Grabowski, E.J.J. J. Am. Chem. Soc. **1988**, 110, 6487. (b) Varasi, M.; Walker, K.A.M.; Maddox, M.L. J. Org. Chem. **1987**, 52, 4235. (c) Pautard-Cooper, A.; Evans, S.A. J. Org. Chem. **1989**, 54, 2485. (d) Crich, D.; Dyker, H.; Harris, R.J. J. Org. Chem. **1989**, 54, 257.
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