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The Direct Preparation of Protected Hydrazines from Alcohols Via Mitsunobu Chemistry

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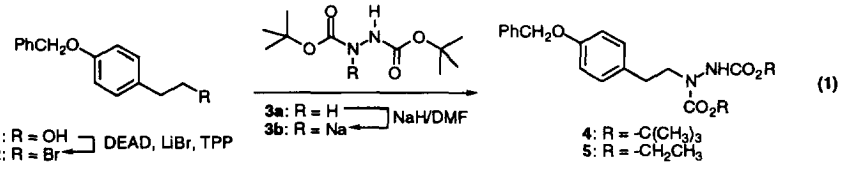
Abstract: *A general method for converting primary and secondary alcohols to protected hydrazines using the Mitsunobu reaction is reported. The reaction of α-hydroxy esters affords dihydrohydrazino esters rather than the expected substitution product.*

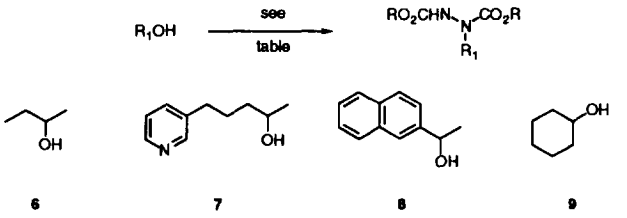
Recently, we required a synthesis of a hydrazine linked via a short carbon chain to a phenol. To this end, hydrazine **4** was prepared from phenethanol **1** (equation 1). Although this sequence did provide the desired molecule, the alkylation of the monosodium salt **3b** with bromide **2**[2] proved to be problematic. Indeed, the yield of this reaction was always on the order of 30-35 % and consequently, an alternative method was sought. Since compound **5** is observed as a by-product of the synthesis of bromide **2**, we hoped that alcohol **1** might be directly converted to hydrazine **4** under the appropriate conditions. In this Communication, we report the optimization of this modification of the Mitsunobu reaction[3,4] and its application to structurally varied alcohols.[5]



(1)

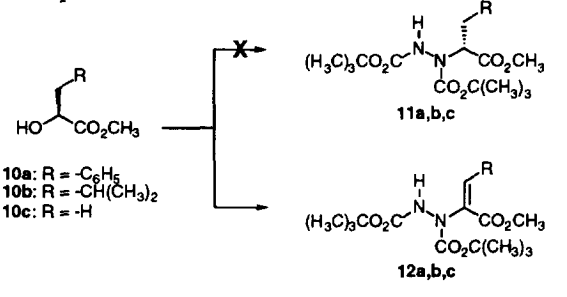
Our results are summarized in Table 1. Reaction of alcohol **1** with DEAD and triphenylphosphine (TPP) under the conditions as described by Falck[2] (entry 1) produced bromide **2** and hydrazine **5** (< 5 %). In the absence of LiBr, di-t-butylazodicarboxylate (DBAD) reacts with alcohol **1** under similar conditions to produce the desired product in 35 % yield (entry 2). This result may be a consequence of low solubility since the reaction became heterogeneous on mixing the reagents and remained so even after refluxing for almost three days. In an effort to enhance solubility, THF was replaced with DMF and, although an improved yield was obtained, these conditions afforded a complicated product mixture (entry 3).[6] This problem was conveniently avoided by premixing alcohol **1** and TPP in THF prior to addition of DBAD (entry 4).[7] Application of these conditions to the secondary alcohols **6-9** was successful (entries 5-8) but the reaction fails with tertiary alcohols. When 1-methylcyclohexanol was subjected to the above conditions, only reduced DBAD and TPP oxide were observed. Presumably elimination of the alkoxyphosphonium salt to volatile olefinic products was the major reaction pathway. Additionally, we tested different azodicarboxylates in this reaction and although DEAD works well (entry 9), the reaction with dibenzylazodicarboxylate (DBeAD) gives low yields (10-20 %) of hydrazine adducts. In general, DBeAD appears to be a less stable azodicarboxylate and yields a much more complicated reaction mixture. The relatively low yield for this reaction reflects this instability as well as the tedious nature of the purification of the final product.

Table 1: Conditions for the conversion of alcohols to protected hydrazines.



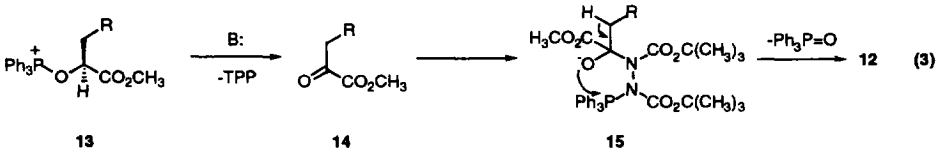
Entry	Conditions	Alcohol	R	% Yield
1	DEAD, TPP, LiBr, THF, 0 °C to RT, 12 h	1	$-C_2H_5$	< 5 %
2	DBAD, TPP, THF, reflux, 63 h	1	$-C(CH_3)_3$	35 %
3	DBAD, TPP, DMF, RT 1 h	1	$-C(CH_3)_3$	59 %[6]
4	DBAD, TPP, THF, 0 °C to RT, 1h	1	$-C(CH_3)_3$	76 %
5	DBAD, TPP, THF, 0 °C to RT, 1h	6	$-C(CH_3)_3$	73 %
6	DBAD, TPP, THF, 0 °C to RT, 1h	7	$-C(CH_3)_3$	71 %
7	DBAD, TPP, THF, 0 °C to RT, 1h	8	$-C(CH_3)_3$	85 %
8	DBAD, TPP, THF, 0 °C to RT, 1h	9	$-C(CH_3)_3$	69 %
9	DEAD, TPP, THF, 0 °C to RT, 1h	1	$-C_2H_5$	72 %

We also investigated the application of this modified Mitsunobu reaction to the synthesis of amino acids, a subject that has received considerable attention in recent years.[8] Specifically, we hoped that enantiomerically pure α-hydroxy esters could be converted to protected α-hydrazino esters of opposite chirality.[9] Subsequent transformation to the corresponding amino acid is precedented.[10] However, when methyl-*S*-2-hydroxy-3-phenyl propanoate (**10a**) was reacted under the described conditions, the isolated product was not the expected hydrazine **11a**, but rather the unsaturated ester **12a** (equation 2). The structure of **12a** was further corroborated by hydrogenation (H_2/10 % Pd-C) to the racemic hydrazino ester.[11] This reaction fails to produce the desired product **11** with methyl-*S*-2-hydroxy-4-methyl pentanoate (**10b**) and *S*-methyl lactate (**10c**).[12] Attempts to alter the reaction course by either lowering the reaction temperature or switching to polar aprotic solvents were unsuccessful.



(2)

We propose the following mechanism for the formation of compounds **12a-c**. Alkoxy phosphonium salt **13** is deprotonated by the phosphine adduct of DBAD to displace TPP, generating ketone **14**, via a Swern-type oxidation (equation 3).[13] Further reaction of α-keto ester **14** with the DBAD adduct gives alkoxide **15** which, after N to O transfer of TPP, proton exchange, and loss of TPP oxide, yields the dihydrohydrazino esters **12**.



In summary, Mitsunobu conditions have been described for the one pot conversion of primary and secondary alcohols to protected hydrazines using either DBAD or DEAD. Unfortunately, α-hydroxy esters are not suitable substrates for this reaction.

Acknowledgments: We thank members of the Physical Chemistry Department, Hoffmann-La Roche, Inc. for the determination of the spectral and microanlytical data for the compounds reported herein.

References:

[1] Post-doctoral fellow 1991-1992; current address: Wyeth-Ayerst Research, Pearl River, NY, 10965.

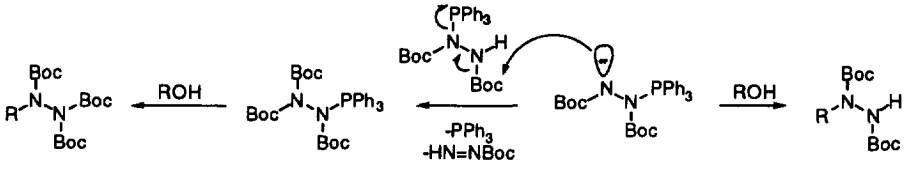
[2] Manna, S.; Falck, J. R. *Syn. Comm.* **1985**, *15*, 663-668.

[3] Mitsunobu, O. *Synthesis* **1981**, 1-28.

[4] For mechanistic investigations of the Mitsunobu reaction see: Pautard-Cooper, A.; Evans, S. A. *J. Org. Chem.* **1989**, *54*, 2485-2488; Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257-259; Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487-6491; Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235-4238.

[5] A literature search revealed two closely related transformations. The first reported the synthesis of diethyl N-allyl hydrazinedicarboxylate en route to phosphate esters, see: Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Japan* **1967**, *40*, 935-939. The second report describes the synthesis of N-glycosyl-1,2-hydrazinedicarboxylates, see: Grynkiewicz, G.; Jurczak, *J. Carbohyd. Res.* **1975**, *43*, 188-191. Weinreb and others report the alkylation of DEAD under Mitsunobu conditions as a byproduct (18 %) in: Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709-5712. For the alkylation of glycine amides under Mitsunobu conditions, see Talaga, P.; Konig, W. *Tetrahedron Lett.* **1992**, *33*, 609-610.

[6] This reaction yielded the desired product **4** and compound **iv** (R = 4-PhCH$_2$O-C$_6$H$_4$-CH$_2$CH$_2$-; 40 %). Falck's procedure stipulated that the azodicarboxylate and TPP were to be premixed for twenty minutes prior to the addition of any other reagents. When this was done in DMF, two molecules of phosphine adduct **i** react to generate species **ii** which then reacts further to afford **iv**. That this is a competitive pathway for adduct **i** is evidenced by the 60:40 mixture of **iii** and **iv** produced.



[7] **General Procedure:** Alcohol **1** (1 mmol) and TPP (2.5 mmol) were dissolved in dry THF (7 mL), cooled to 0° C under Ar and treated with a THF solution (3 mL) of di-t-butylazodicarboxylate (DBAD; 2.45 mmol). The reaction temperature was maintained at 0 °C for twenty minutes and then warmed to RT over forty minutes. The reaction was then diluted with water (15 mL) and CH_2Cl_2 (15 mL) and the layers were separated. The aqueous phase was extracted with ether (1 x 25 mL) and the combined organic layers were washed with water (1 x 25 mL), brine (1 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product on silica gel, eluting with EtOAc:Hex gave protected hydrazine **4**. All new compounds gave satisfactory spectral and microanalytical data.

[8] Gennari, C.; Colombo, L.; Bertolini, G.; *J. Am. Chem. Soc.* **1986**, *108*, 6394-6395; Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395-6397; Trimble, L.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397-6399; Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525-5540.

[9] For an interesting application of α-hydrazine esters to peptide chemistry, see: Lecoq, A.; Marraud, M.; Aubry, A. *Tetrahedron Lett.* **1991**, *32*, 2765-2768.

[10] Di-t-butylhydrazinedicarboxylates have been converted into amines in one pot with acid and hydrogen, see: Genet, J. P.; Juge, S.; Mallart, S. *Tetrahedron Lett.* **1988**, *29*, 6765-6768; Oppolzer, W.; Moretti, R. *Helv. Chim. Acta* **1986**, *69*, 1923-1926. Substituted ethyl-1,2-hydrazinedicarboxylates have been converted to carboethoxyamines, see: Taylor, E. C.; Sowinski, F. *J. Org. Chem.* **1974**, *39*, 907-910.

[11] The hydrogenation product gave an identical NMR spectrum to that of an authentic sample prepared from methyl 3-phenylpropanoate, LDA, and DBAD.

[12] Mandelate esters gave products that decomposed on exposure to silica gel precluding identification.

[13] The crude product mixture of these reactions was contaminated with substantial amounts of TPP whereas in the examples in Table 1 little or no TPP was found.

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