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N-tert-Butoxycarbonylaminophthalimide, a versatile reagent for the conversion of alcohols into alkylated *tert*-butylcarbazates or hydrazines via the Mitsunobu protocol

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Abstract

An efficient two-step method has been developed for the conversion of alcohols to substituted hydrazines. The use of *N-tert*-butoxycarbonylaminophthalimide as an acid partner in Mitsunobu reactions with a variety of alcohols permits the synthesis of the corresponding monoalkylated *tert*-butylcarbazates and hydrazines.

Keywords: Mitsunobu reactions; hydrazines; alkylation.

The Mitsunobu reaction, which performs *O*- and *N*-alkylation under mild conditions, has been used for the conversion of alcohols into a wide range of derivatives including esters, amines, imides, azides, etc.[1] The reaction proceeds via condensation of an alcohol ROH with an acid HA aided by the use of diethylazodicarboxylate (DEAD) and triphenylphosphine.[1a] It has been reported[2] that the success of the Mitsunobu reaction is highly dependent upon the nature of the acid partner which must be strong enough to be easily deprotonated and not be too hindered to allow nucleophilic attack with inversion of configuration in the SN_2 step. As a result, cyclic or acyclic imides,[1a,2] oxamates[3] and sulfonylcarbamates[4] have been successfully used as nitrogen nucleophiles to yield amine derivatives. Ragnarsson and colleagues[2a] reported that imidodicarbonates can be used to prepare amino acids in synthetic protocols that utilize the Mitsunobu reaction and also confirmed that the yield from the reaction is clearly dependent upon the electronic and steric nature of the acid partner.

As a part of our studies aimed at developing a synthetic method for producing monolabelled isoniazide,[5] we performed the synthesis of 1,1-bis(*tert*-butoxycarbonyl) aminophthalimide **2** using *N*-aminophthalimide **1** as a starting material. We also showed that **2** could be easily mono deprotected thus producing *N-tert*-butoxycarbonylaminophthalimide **3**[5b] (Scheme 1).

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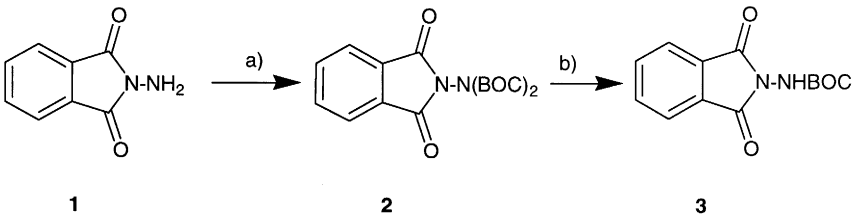
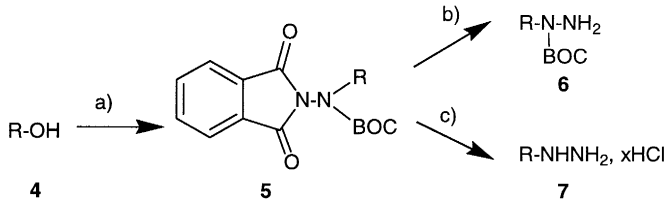


Scheme 1. (a) $(BOC)_2O$, DMAP, Et_3N, THF, rt, 2 h, 65%; (b) CF_3COOH, CH_2Cl_2, rt, 48 h, 75%

Compound **3** may be considered as a triprotected hydrazine, since one could envisage that both the phthaloyl and the *tert*-butoxycarbonyl groups may potentially be removed. In addition, the presence of three electron-withdrawing acyl groups increases the acidity of the hydrazinyl proton whilst the incorporation of two of the three acyl groups into the phthaloyl moity reduces steric hindrance. In light of the above we postulated that compound **3** could act as a good acid partner in a Mitsunobu reaction for a mild and stereospecific means of converting alcohols to substituted hydrazines. The latter are generally obtained by reduction of the corresponding hydrazones,[6] or by using triprotected hydrazines under PTC conditions as recently described,[7] or even by direct alkylation[8] of the hydrazine itself.

Here we report, for the first time, the rapid and efficient syntheses of monoalkylated *tert*-butylcarbazates **6** and hydrazines **7**, in only two steps, respectively, by using alcohols **4** as starting materials in a Mitsunobu reaction (as specified in Scheme 2).



Scheme 2. Reagents: (a) Compound **3**, 1 equiv.; DEAD, 1.5 equiv.; PPh_3, 1.5 equiv., 0.5 h; (b) $MeNHNH_2$, 1.5 equiv., THF; (c) (1) $MeNHNH_2$, 1.5 equiv., THF; (2) filtration; (3) HCl gas, anhydride Et_2O

Using this methodology, as summarized in Table 1 (step a), when a range of alcohols **4** were subjected to the usual Mitsunobu conditions[1a] for 0.5 hours in the presence of **3**, the corresponding products **5** were obtained with good yields regardless of the nature of the starting alcohol (methanol, primary, secondary, benzylic or allylic). Dephthaloylation reactions (step b) were performed by treating a solution of **5** in THF with 1.5 equiv. of methylhydrazine over 0.5 hours at −20°C. Reaction mixtures were then brought to room temperature until completion (monitored by TLC). The use of methylhydrazine, employed to avoid the formation of a complex with the free amine,[11] as reported elsewhere, resulted in a very clean reaction compared to hydrazine hydrate or phenylhydrazine which gave poor results in these studies. Following filtration to remove *N*-methylphthalhydrazide which precipitates as a by-product, the desired *N*-alkylated *tert*-butylcarbazates **6** were isolated and purified by column chromatography on neutral alumina gel. Removal of the BOC group can be performed without purification of **6** (step c) using HCl gas in anhydrous ether. Under these conditions, monoalkylated hydrazines could be isolated as hydrochloride salts **7**.

In summary, we have shown that alcohols can be efficiently converted into substituted hydrazines **7** utilizing *N*-*tert*-butoxycarbonylaminophthalimide **3**. These substituted hydrazines can also be isolated in a BOC-protected form as compounds **6** that subsequently may be used in other multistep synthetic protocols. Moreover, using the strategy we have developed to obtain compound **3**,[5b] singly labelled substituted hydrazines could be obtained using commercially available potassium [^{15}N]phthalimide as

Table 1

Substrate	Step a	Step b		Step c
4 R =	**5** yield %[a]	Time (h)	**6** yield %[b]	**7** yield %[b]
4a $-CH_3$	97	70	65	76[c]
4b $-(CH_2)_5-CH_3$	86	24	81	96[d]
4c $-CH_2-C_6H_5$	83	15	96	84[d]
4d $-CH(CH_3)_2$	77	6.5	63	96[e]
4e $-CH_2-CH=CH_2$	67	15	89	97[e]
4f -cyclopentyl	85	24	85	92[d]

a) Isolated yields calculated from **3**. b) Isolated yields calculated from **5**. c) Compounds **7a** has been obtained as sesquihydrochloride sesquihydrate salt.[9] d) **7b, 7c** and **7f** have been obtained as monohydrochloride salts.[6] e) **7d** and **7e** have been obtained as dihydrochloride salts.[10]

a starting material. The use of *N-tert*-butoxycarbonylaminophthalimide **3** in other synthetic applications is currently under investigation.

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