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N-Boc Ethyl Oxamate : a New Nitrogen Nucleophile for Use in Mitsunobu Reactions.

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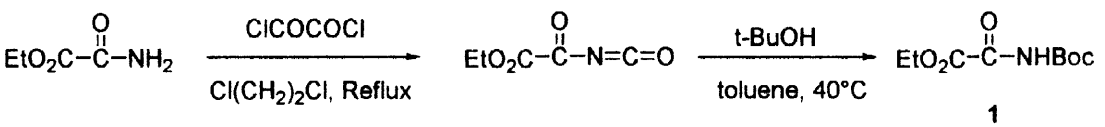
Abstract : N-Boc ethyl oxamate can be directly coupled with primary and secondary alcohols under Mitsunobu conditions to afford various N-Boc amines after mild deprotection.

Phthalimide is generally applied to N-alkylation with alcohols under Mitsunobu conditions. This synthesis of primary amines suffers from the disadvantage that the standard conditions for cleavage of phthaloyl protection are undesirably vigorous[1]. This has prompted investigations[2] of a number of alternatives to phthalimide such as imidodicarbonates[3], acylcarbamates[4] and sulfonylcarbamates[3a,5]. These compounds yield N-alkyl derivatives but so far the procedures required reagents which are not conveniently accessible or need rather drastic conditions of deprotection.

Herein we report the synthesis of the N-Boc ethyl oxamate **1** that can be used in Mitsunobu reactions and be readily transformed into a N-Boc protected amine. Compound **1** was easily prepared as shown in scheme 1. Reaction of ethyl oxamate with oxalyl chloride gave ethyloxalyl isocyanate[6] (82% yield) which when treated with t-butanol provided **1** with a quantitative yield.



Scheme 1

A recent study on a series of imidodicarbonates[3], used in Mitsunobu reactions, noticed that the yields obtained correlated remarkably well with the pK_a of the reagent. For example, in the case of ethyl lactate used as alcohol, the authors concluded that a pK_a in DMSO of around 13.5 (9 in H_2O[7]) or lower was required for the reagent in order to achieve a satisfactory reaction under the usual experimental conditions. Since a pK_a of 8.8 for the N-Boc ethyl oxamate **1** was determined[8], we could expect that our compound **1** was sufficiently acidic to give good yields in Mitsunobu reactions.

Effectively, treatment of various alcohols, at room temperature, with 1.2 equivalents of **1** under Mitsunobu conditions[9] gave the expected N-Boc ethyl oxamates **2** (Scheme 2). As shown in Table 1, the obtained yields are good. For example, 3-bromo propanol (entry b) led to protected amine **2b** with 91% yield. The results are slightly lower for secondary alcohols (entries d and e).

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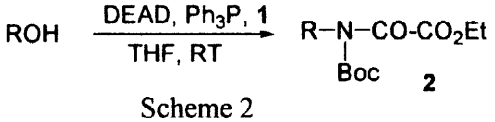


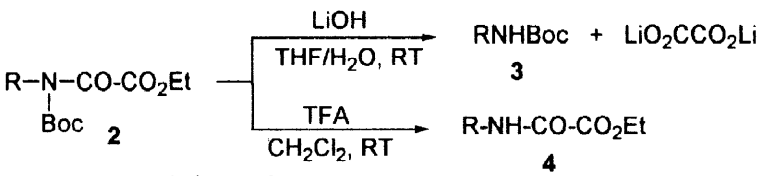
Scheme 2

Table 1. Conversion of alcohols to N-Boc ethyl oxamates **2.**

entry	ROH	Yield [a] (%) of **2**	entry	ROH	Yield [a] (%) of **2**
a	CH_3CH_2OH	80	d	Ph-$CH(CH_3)$-OH	72
b	$Br(CH_2)_3OH$	91	e	(S)-EtO_2C-$CH(CH_3)$-OH	82
c	Ph-CH=CH-CH_2-OH	93			

a. Yield of isolated product after purification by column chromatography

Interest of reagent **1** appears especially during the deprotection of product **2**. The oxamate group is very sensitive to weak nucleophiles and it is possible, therefore, to accede to N-Boc amines by simple treatment with a weak base like LiOH, at room temperature[10] (quantitative yields). The isolation is, otherwise, particularly easy because of the solubility of the lithium salt in water. Using these conditions, it should be possible to prepare protected optically active α-aminoacids from α-hydroxyesters. Effectively, L-ethyl lactate (entry e) was directly converted to N-Boc D-alanine **3e** without racemisation[11].



Scheme 3

On the other hand, selective deprotection of the Boc group, by treatment of **2** with trifluoroacetic acid (TFA), is a good way to N-substituted oxamates **4** (Scheme 3).

In summary, the results described above demonstrate that N-Boc ethyl oxamate **1** is an excellent nucleophile in Mitsunobu couplings. Particularly mild conditions can be used for the final obtention to protected N-Boc amines.

References and Notes

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8. The p*K*a determination was performed at 25°C using potentiometric titration of the NH-acid, in a 50/50 H_2O/EtOH solution, with a solution of KOH.
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10. To a solution of **2** (2 mmol) in THF (4 mL) ,a solution of LiOH (6 mmol) in H_2O (3 ml) was added at room temperature. After 3 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and concentrated in vacuo to give product **3**.
11. **3e** : $[\alpha]_D^{20}$ +26.5 (*c* 0.7, MeOH). Lit.[12], $[\alpha]_D^{20}$ +25.2 (*c* 1, MeOH).
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