

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

Fabienne Berrée,* Gwendal Michelot and Maurice Le Corre

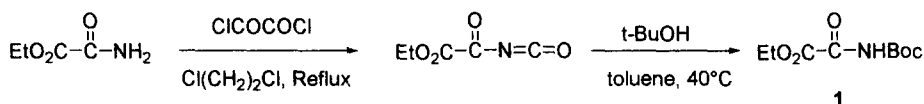
Laboratoire de Synthèse Organique, Associé au CNRS.
Avenue du Général Leclerc, 35042 Rennes, France.

Received 29 June 1998; accepted 3 September 1998

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.
© 1998 Elsevier Science Ltd. All rights reserved.

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 vigorous¹. This has prompted investigations² of a number of alternatives to phthalimide such as imidodicarbonates³, acylcarbamates⁴ 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 isocyanate⁶ (82% yield) which when treated with t-butanol provided **1** with a quantitative yield.



Scheme 1

A recent study on a series of imidodicarbonates³, 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 determined⁸, 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 conditions⁹ 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).

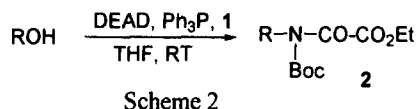
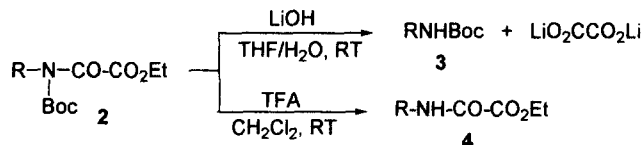


Table 1. Conversion of alcohols to N-Boc ethyl oxamates 2.

entry	ROH	Yield ^a (%) of 2	entry	ROH	Yield ^a (%) of 2
a	CH ₃ CH ₂ OH	80	d	Ph-CH(CH ₃)-OH	72
b	Br(CH ₂) ₃ OH	91	e	(S)-EtO ₂ C-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 temperature¹⁰ (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 racemisation¹¹.



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

- Gibson, M. S. and Bradshaw, R. W. *Angew. Chem., Int. Ed. Engl.* **1968**, 7, 919-930.
- For a review see: Ragnarsson, U. and Grehn, L. *Acc. Chem. Res.* **1991**, 24, 285-289.
- (a) Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L. and Ragnarsson, U. *J. Org. Chem.* **1991**, 56, 7172-7174. (b) Degerbeck, F.; Fransson, B.; Grehn, L. and Ragnarsson, U. *J. Chem. Soc. Perkin Trans 1* **1992**, 245-253. (c) Chong, J. M. and Park, S. B. *J. Org. Chem.* **1993**, 58, 7300-7303.
- Koppel, I.; Koppel, J.; Leito, I.; Pihl, V.; Wallin, A.; Grehn, L. and Ragnarsson, U. *J. Chem. Soc. Perkin Trans 1* **1993**, 655-658.
- Campbell, J. A. and Hart, D. J. *J. Org. Chem.* **1993**, 58, 2900-2903.
- Speziale, A.J. and Smith, L.R. *J. Org. Chem.* **1962**, 27, 3742-3743.
- Koppel, I.; Koppel, J.; Leito, I.; Pihl, V.; Grehn, L. and Ragnarsson, U. *J. Chem. Res. (S)* **1994**, 212-213.
- The pK_a determination was performed at 25°C using potentiometric titration of the NH-acid, in a 50/50 H₂O/EtOH solution, with a solution of KOH.
- Mitsunobu, O. *Synthesis* **1981**, 1-28. Conditions used: ROH (1 eq); DEAD, PPh₃ and 1 (1.2 eq), THF, RT, 16 h.
- To a solution of 2 (2 mmol) in THF (4 mL), a solution of LiOH (6 mmol) in H₂O (3 mL) was added at room temperature. After 3 h, the reaction mixture was diluted with H₂O and extracted with CH₂Cl₂. The organic layer was dried over sodium sulfate and concentrated in vacuo to give product 3.
- 3e: $[\alpha]_D^{20} +26.5$ (c 0.7, MeOH). Lit.¹², $[\alpha]_D^{20} +25.2$ (c 1, MeOH).
- Moriniere, J. L.; Danree, B.; Lemoine, J. and Guy, A. *Synth. Commun.* **1988**, 18, 441-444.