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From vicinal azido alcohols to Boc-amino alcohols or oxazolidinones, with trimethylphosphine and Boc_2O or CO_2

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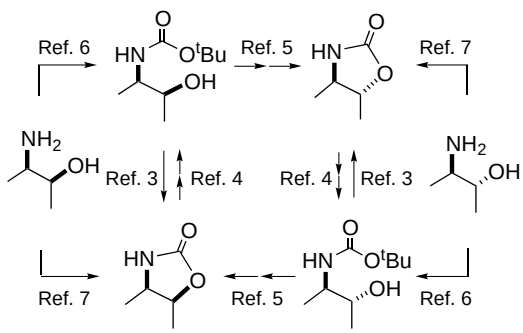
Abstract—A practical solution to the problem of converting directly 1,2-azido alcohols to Boc-amino alcohols, without recourse to catalytic hydrogenation, involves the use of Me_3P/Boc_2O in THF (or CH_2Cl_2) and aqueous NaOH at rt (90–98% yields). The same azido alcohols can be converted in one-pot to the corresponding oxazolidinones with $Boc_2O/DMAP/Me_3P$ or even better with CO_2 and Me_3P under basic catalysis (91–96% yields).

Vicinal amino alcohols have an outstanding significance as chiral ligands and as precursors of chiral oxazolines and oxazolidin-2-ones;[1] applications of these oxazolidinones as chiral auxiliaries[1] and as pharmaceuticals[2] are well-known. In this context, very recent papers 'connecting' Boc-amino alcohols and oxazolidinones (Scheme 1) deserve to be mentioned;[3–5] for instance, activation of the hydroxyl near the Boc-amino group causes an intramolecular attack that affords generally the epimeric oxazolidinone.[5] Several methods are available for both the conversion of amines to *N*-Boc derivatives[6] and of vicinal amino alcohols to oxazolidinones.[7] The conditions for the reverse reactions (hydrolyses) are well established, and *tert*-butyl carbamates (i.e. *N*-Boc derivatives) may be interconverted with other carbamates through isocyanates.[8] Taken all together this constitutes a chart or road map that links all the species shown in Scheme 1 with isocyanates or isocyanate precursors and with other carbamates.

A standard entry to non-natural amino-protected alcohols involves a selective epoxidation of a double bond, ring opening by an azide ion or an azido-transfer reagent,[9] hydrogenation (or alternative hydride-based reduction) of the azido group and amine protection. The catalytic hydrogenation step is often performed in the presence of the protection reagent,[10] but this protocol may be incompatible with polyfunctional substrates containing other unsaturations, sulphur atoms, sensitive protecting groups (*Z*), etc.[10e,f]

In such cases, the Staudinger reaction between phosphines and azides[11] in the presence of RCOX or ROCOX could be the method of choice.[12] To ensure fast reactions, mild conditions and easy work-up (elimination of phosphine oxides by extraction with water), we utilised trimethylphosphine or triethylphosphine.[12] In this connection, we tried to convert directly[13] β-azido alcohols[14] to *tert*-butyl carbamates by using Me_3P and a common reagent like di-*tert*-butyl dicarbonate, $(^tBuOCO)_2O$, i.e. Boc_2O, or to oxazolidinones, at will, but the yields were often too low with the formation of several byproducts. We focused our efforts on understanding the causes of the erratic results, with the purpose of devising procedures for driving so many concomitant reactions. We describe here the direct conversion of vicinal azido alcohols to *N*-Boc derivatives or to oxazolidinones by stirring the substrates and appropriate reagents at rt. Thus, the present report complements the works previously mentioned.[3–10]



Scheme 1.

Keywords: amines; azides; carbamates; oxazolidinones; protecting groups.

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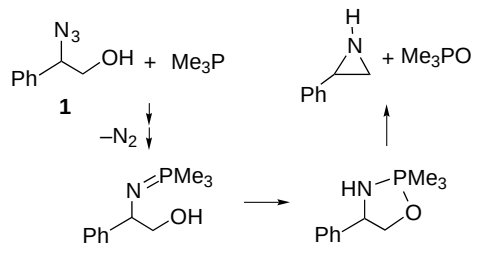
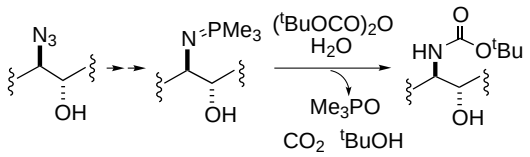
First of all, let us summarise the shortcomings of the phosphine-based approach. (i) One-pot reaction of sterically crowded azides with phosphines and Boc_2O gives, after the final work-up, poor-to-moderate yields of *N*-Boc derivatives, carbodiimides being the major products.[15] In our hands, 1-phenylethyl azide, $PhCH(Me)N_3$, always afforded carbodiimide PhCH(Me)N=C=NCH(Me)Ph in significant amounts independent of the temperature, the order of addition of the reagents or the amount of trialkylphosphine.[12d] The carbon atom of this carbodiimide group must come from Boc_2O, probably from its partial decomposition to CO_2.[16,17] (ii) It is known that vicinal azido alcohols and Ph_3P give five-membered intermediates (oxazaphospholidines) that may afford aziridines spontaneously.[18] We have observed that with Me_3P formation of 2-phenylaziridine from 2-azido-2-phenylethanol (**1**) easily takes place (Scheme 2).[18g] Thus, there is always a chance for the formation of aziridine derivatives.[19]

Therefore, when the azide group of the azido alcohol is linked to a secondary or tertiary carbon atom, it is understandable that its reaction with Me_3P and Boc_2O gives poor yields of the carbamate, as all the reactions just mentioned may occur.

To obtain excellent yields of Boc-amino derivatives from azido alcohols, Me_3P and Boc_2O under very mild conditions, it seemed essential to us to avoid the formation of CO_2 (by removing or destroying its sources) or to trap the CO_2 molecules as soon as they appeared (otherwise they would immediately react with the phosphazene which was being formed to give isocyanates and derivatives such as carbodiimides, oxazolidinones, etc.),[16,17] as well as to avoid the formation of oxazaphospholidines or to cleave it rapidly (otherwise aziridines and derivatives thereof would be formed). We wanted to perform the reaction in one-pot, mixing substrate and reagents together, including water if possible, in which case not only did a certain percentage of CO_2 precursor(s) slowly appear in the reaction flask, but also one equivalent amount of CO_2 could be eventually delivered, as deduced from the reaction stoichiometry (see Scheme 3).



Scheme 2.



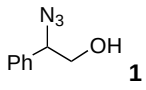
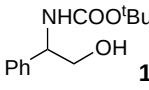
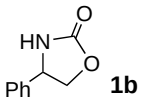
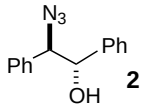
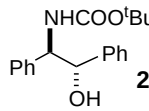
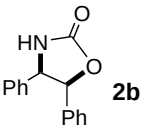
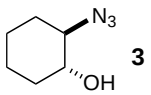
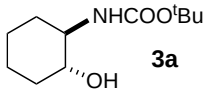
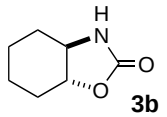
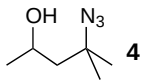
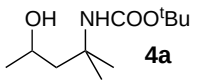
Scheme 3.

After many trials with 1-phenylethyl azide as a model[20] and with azido alcohol **1**, reaction of vicinal azido alcohols **1**–**3** (and, for comparison, of 1,3-azido alcohol **4**) was performed with Me_3P (1.2–1.4 equiv.) and Boc_2O (1.1 equiv.), in THF at rt in the presence of 1 M aq. NaOH (1.1 equiv.). Yields of carbamates **1a**–**3a** were excellent, as shown in Table 1, within a few hours. It is worthy to mention that the presence of a basic medium, to avoid the protonation of $^tBuOCOO^-$ to $^tBuOCOOH$ (which would decompose even more rapidly affording CO_2) and/or to remove CO_2 as HCO_3^- or CO_3^{2-}, is essential for success.[17,20] Protection of **3** was repeated in CH_2Cl_2–H_2O, i.e. with the two layers completely immiscible, by shaking for 3 h, from 0 to 20°C, a mixture of **3**, Me_3P, Boc_2O and NaOH as above, with the same excellent result.

On the other hand, to convert vicinal azido alcohols into oxazolidinones in a one-pot reaction, it was apparently required that isocyanates (Scheme 4) were formed more rapidly than oxazaphospholidine intermediates shown in Scheme 2. This turned out to be the case when **1** was treated in anhydrous THF at rt with different Boc_2O/DMAP/Me_3P ratios. Yields of oxazolidinone **1b** ranged between 50 and 72% when the addition order to the THF-containing flask was Boc_2O, DMAP, **1** and Me_3P. The best yield (72% of **1b**, plus 15% of 2-amino-2-phenylethanol) was obtained with 1.2 mmol of DMAP, 1.2 mmol of Boc_2O, 1.0 mmol of **1** and 2.0 mmol of Me_3P, in 10 mL of THF. Larger excesses of DMAP and/or Boc_2O did not enhance that yield. By sharp contrast, when 1.0 equiv. of H_2O was added to anhydrous THF, it was not necessary to use an excess of DMAP or Me_3P. In practice, we added the following reagents to the moist THF: Boc_2O (1.2 equiv.), DMAP (0.25 equiv.), **1** and Me_3P (1.2 equiv.). The yield of **1b** was 75%. Thus, a high percentage of the CO_2 molecules generated from the catalysed hydrolysis of Boc_2O react with the phosphazene that is being generated. It is likely that the yield is not higher because the cyclisation of hydroxy isocyanate to oxazolidinone is not very rapid, which gives other reactions a chance. The paradox is that a controlled addition of water plays a significant role in favour of the hydroxy isocyanate.

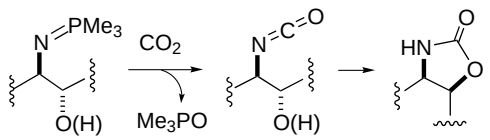
To further improve the oxazolidinone yields, it seemed reasonable at first sight to increase the amount of CO_2 in the medium, looking for a ready formation of isocyanate[21] and its cyclisation to oxazolidinone (Scheme 4). Thus, a solution of **1** in THF at −78°C was saturated with a stream of CO_2, Me_3P was added and the temperature was allowed to rise to rt maintaining a positive CO_2 pressure. However, the yield of **1b** reached only 65–70%. This result indicates that it does not matter whether an excess of CO_2 or a controlled amount from Boc_2O/DMAP/H_2O is used.

Table 1. Conversion of azido alcohols **1**–**4** to carbamates **1a**–**4a**, and of **1**–**3** to oxazolidinones **1b**–**3b**

Azido alcohol	Reagents	Product	Yield	Reagents	Product	Yield
 **1**	Me_3P/Boc_2O[a]	 **1a**	98%	CO_2/Me_3P[b]	 **1b**	95%
 **2**	Me_3P/Boc_2O[a]	 **2a**	90%	CO_2/Me_3P[b]	 **2b**	96%
 **3**	Me_3P/Boc_2O[a]	 **3a**	95%	CO_2/Me_3P[b]	 **3b**	91%
 **4**	Me_3P/Boc_2O[a]	 **4a**	85%			

[a] In THF, plus aq NaOH, at rt. **Typical procedure:** A solution of Me_3P in THF (ca. 1 M, 1.4 mL, ca. 1.4 mmol) is added to a vigorously stirred biphasic solution of the azido alcohol (1.0 mmol) in THF (3 mL) and degassed aqueous NaOH (1 M, 1.1 mL, 1.1 mmol) at rt; a solution of Boc_2O (240 mg, 1.1 mmol) in THF (5 mL) is then added. Three to four hours later the mixture is quenched by addition of a phosphate buffer solution (pH 7). Extraction with CH_2Cl_2, drying of the organic extracts, filtration, removal of the solvent, and purification of the residue by column chromatography on silica gel (98:2 CH_2Cl_2–MeOH) afford the Boc-amino alcohols **1a–4a**.

[b] In THF, from –78 °C to rt. **Typical procedure:** NaH (10 mg of Fluka 55–65% suspension, 0.23–0.27 mmol), rinsed with hexane, or BuLi in hexanes (ca. 1.6 M, 0.15 mL, ca. 0.25 mmol), is added to a solution of the azido alcohol (1.0 mmol) in THF (10 mL) at –78 °C. A stream of CO_2 (from solid CO_2, through anhydrous $CaCl_2$) is bubbled for ca. 30 min, while a balloon connected to the flask is filled with the gas, and a solution of Me_3P in THF (ca. 1 M, 1.4 mL, ca. 1.4 mmol) is added via syringe. The mixture is stirred at rt for 3–4 h. The solution is quenched with a phosphate buffer solution and extracted with CH_2Cl_2. After drying and filtering, removal of the solvent under vacuum affords chromatograpically and spectroscopically pure oxazolidinones **1b–3b**.



Scheme 4.

On the other hand, when cold solutions of vicinal azido alcohols **1**–**3** were partially deprotonated, saturated with CO_2 and treated with Me_3P, pure oxazolidinones **1b**–**3b** were obtained in 91–96% yields (see Table 1) after a simple extraction. Addition of 25 mol% of NaH or BuLi to cold THF solutions of **1**–**3** was sufficient, apparently, to later favour the intramolecular attack to the isocyanate.[22]

In summary, in the direct reaction of azido alcohols with phosphines and Boc_2O, by reducing to a minimum the CO_2 source in the reaction medium, *N*-Boc-amino alcohols can be obtained in excellent yields. On the other hand, in the presence of CO_2 (from the Boc_2O decomposition or by using external CO_2 instead), oxazolidinones are obtained. If the reaction follows its own way, the several alternative pathways give rise to complex mixtures that are not useful from a synthetic point of view. The simple experimental protocols reported here offer versatile solutions to the problem of the reduction and protection in situ of vicinal azido alcohols when catalytic hydrogenation is inappropriate.

Acknowledgements

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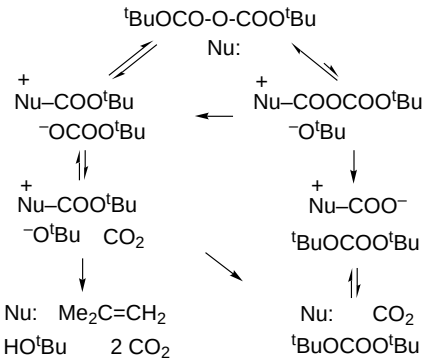
13. By reaction of phosphazenes (or of phosphatriazenes, see Ref. 12a) as soon as formed with the protection reagent already present in the flask, instead of by the known procedure of hydrolysis (of phosphazenes to amines) followed by protection. When this protection cannot be performed in situ owing to the reagent incompatibility with the aqueous medium, when amines may react with other groups, etc. (see Refs. 10a and 12e), direct conversion of azides to protected amines can be advantageous.
14. Vicinal amino alcohols, or 1,2-amino alcohols, are often so-called β-amino alcohols but other authors name them α-amino alcohols, owing to their relationship with α-amino acids.
15. (a) Afonso, C. A. M. *Tetrahedron Lett*. **1995**, *36*, 8857–8858; (b) Afonso, C. A. M. *Synth. Commun*. **1998**, *28*, 261–276.
16. The carbodiimide arises likely from the reaction of isocyanate PhCH(Me)NCO with remaining phosphazene. Since this carbodiimide is formed in significant amounts when Boc_2O is used, but not with BocON (2-*t*-butoxycarbonyloxyimino-2-phenylacetonitrile), nor with a previously prepared BocON/DMAP mixture (as a source of $DMAP^+$–COO^tBu), nor with other carboxylating/acylating agents (Ref. 12e), it can be assumed that the isocyanate comes from the presence in the reaction medium of CO_2 or a closely related precursor. In fact, Boc_2O, a dicarbonate, is an inherent source of CO_2. For an example, see: (a) Molina, P.; Alajarín, M.; Sánchez-Andrada, P. *Tetrahedron Lett*. **1993**, *34*, 5155–5158. For a related reaction (conversion of poorly nucleophilic amines to isocyanates with Boc_2O/DMAP) and outstanding mechanistic studies, see: (b) Knölker, H. J.; Braxmeier, T.; Shlechtingen, G. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2497–2500. Review on DMAP-catalysed acylations: (c) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res*. **1998**, *31*, 494–501. Review on Boc_2O: (d) *Encyclopedia of Reagents for Organic Synthesis;* Paquette, L. A., Ed.; Wiley: Chichester, 1995; Vol. 3. For other relevant works, see: (e) Kemp, D. S.; Curran, T. P. *J. Org. Chem*. **1988**, *53*, 5729–5731 (isolation of $R_2NCOOCOO^tBu$ in a special case); (f) Saylik, D.; Horvath, M. J.; Elmes, P. S.; Jackson, W. R.; Lovel, C. G.; Moody, K. *J. Org. Chem*. **1999**, *64*, 3940–3946 (isocyanates from primary amines and CO_2).
17. In our hands, Boc_2O (Fluka, ≥99.5% purity, checked by ^{13}C NMR) gave bubbles, clearly seen at rt at concentrations higher than 0.1 M, when mixed with 2 equiv. of DMAP and also (but more smoothly) with 1:1 DMAP–Me_3P or with 2 equiv. of Me_3P in anhydrous THF. The nucleophile-catalysed decomposition of Boc_2O, in general, might be summarised as in Scheme 5 (further possible reactions of intermediates with Nu, or between species such as Nu^+–COO^- and Nu^+–COO^tBu, are not included for the sake of simplification), with preferred courses depending on the features of each substrate, temperature,

solvent polarity, basicity of Nu, etc. It is reasonable that, in mixing sterically crowded azides with phosphines and Boc_2O, at the beginning the hindered phosphazene molecules behave as Nu of Scheme 5, but later the remaining ones may react preferably with the more active species that appear in the medium (such as CO_2 arising either from $M^{+-}OCOO^tBu$ or from the decomposition of any EWG–COO^tBu species). Moreover, if the solvent is not anhydrous, the nucleophile-catalysed decomposition of Boc_2O is more rapid; the hydrolysis of the main intermediate (Nu^+–$COO^tBu^-OCOO^tBu$) is expected to afford two ^{t}BuOCOOH molecules (i.e. 2 mol of CO_2 and ^{t}BuOH per mol of water).



Scheme 5.

18. Illustrative examples: (a) Chakraborty; T. K.; Jayaprakash, S.; Srinivasu, P.; Chary, M. G.; Diwan, P. V.; Nagaraj, R.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron Lett*. **2000**, *41*, 8167–8171; (b) Wipf, P.; Venkatraman, S.; Miller, C. P. *Tetrahedron Lett*. **1995**, *36*, 3639–3642; (c) Besse, P.; Veschambre, H.; Chênevert, R.; Dickman, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1727–1744; (d) Ziegler, F. E.; Belema, M. *J. Org. Chem*. **1994**, *59*, 7962–7967. For reviews, see: (e) Tanner, D. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 599–619; (f) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715. For a previous example with Me_3P, the aziridine being formed in practically quantitative yield, see: (g) Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem*. **1998**, *63*, 4545–4550.
19. In practice, when 2-azido-3-phenylpropan-1-ol was treated at rt with Me_3P in THF and two hours later Boc_2O and aqueous NaOH was added, a complex mixture was obtained from which *N*-Boc-2-amino-3-phenylpropan-1-ol (50% yield) and the corresponding *N*-Boc-aziridine (26%) were isolated. Other acylating or carboxylating agents (RCOX or ROCOX) also gave complex mixtures when treated with vicinal azido alcohols and phosphines. For instance: **1**, Me_3P and BocON, in THF at rt, afforded only a 62% yield of the *N*-Boc-amino alcohol (**1a**), as well as several byproducts; **1**, Me_3P and BocON/DMAP gave, after 5 h at rt, **1a** and the corresponding *N*-Boc-aziridine in ca. 1:1 ratio, but not oxazolidinone **1b**. At first sight, the involvement of oxazaphospholidines and aziridines could be circumvented by protection of the hydroxyl group. However, we had noted (Ref. 12b) that α-benzyloxy and α-*t*-butyldimethylsilyloxy phosphazenes gave poor yields of carboxamides in reacting with mixed anhydrides (probably as a consequence of the formation of P-chelated intermediates, the hydrolysis of which was not selective). Protection of the hydroxyl groups as acetates was inappropriate, since acetoxy phosphazenes afforded oxazolines by intramolecular attack; we had to protect 1,2-azido alcohols as *O*-benzoyl derivatives to suppress these aza-Wittig-like reactions. (This is not the case with 1,3-azido alcohols, as protection of the hydroxyl groups either as silyl ethers, as acetates, or as benzoates avoids these concomitant reactions.)
20. In anhydrous THF, i.e. without adding water from the very beginning, the yield of Boc-amine from 1-phenylethyl azide, Me_3P and Boc_2O was only 40% (the major product was the corresponding carbodiimide, as already mentioned). If an excess of water is present, i.e. in THF–H_2O, the highest yield of Boc-amine was 70% (and 10% of the corresponding urea, likely arising from the carbodiimide, was isolated). In the presence of 1.1 equiv. of NaOH (THF–H_2O biphasic solution), the isolated yield of Boc-amine was 92%. According to independent experiments monitored by NMR, hydrolysis of P-containing species is rapid under the reaction conditions and contributes to the success, but the crucial point was the control of ^{t}BuOCOO$^-$ and CO_2 (Ref. 17).
21. The reaction of Ph_3P-derived phosphazenes with CO_2, in refluxing benzene, to give isocyanates in excellent yields is known: (a) Molina, P.; Alajarín, M.; Arques, A. *Synthesis* **1982**, 596–597. For a review, see: (b) Johnson, A. W. *Ylides and Imines of Phosphorus*; Wiley: New York, 1993; p. 428.
22. Trapping of CO_2 as an alkyl carbonate might also be involved.