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One-Pot Conversion of Azides to Boc-Protected Amines with Trimethylphosphine and Boc-ON

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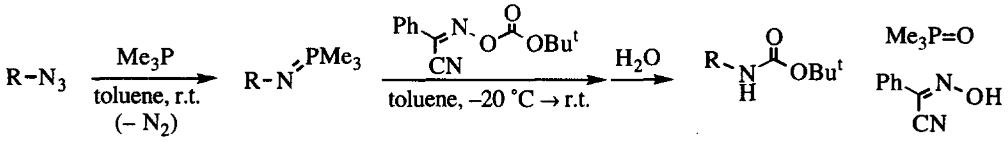
Abstract

Reaction of azides with trimethylphosphine followed by addition of 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON) at –20 °C and stirring at r.t. for 5 h affords the desired Boc-amines in 87–100% yields. Similar yields are obtained by mixing all components together (azide, Me_3P, and Boc-ON) in toluene or THF.

Keywords: Amines; Azides; Carbamates; Phosphazenes; Protecting groups.

Substitution of a leaving group by the azide anion, reduction of the azide to an amine, and protection of the amine as *t*-butoxycarbamate (R-NH-Boc) is a standard process in organic synthesis; Boc is among the most common protecting groups for amines, amino acids, and other nitrogen compounds [1]. To save time and to avoid secondary reactions or losses of material during the isolation of certain amines, the reduction and protection steps are frequently performed in one pot since Saito et al. [2] showed that reduction of several azides with hydrogen-presaturated Pd/C, in the presence of di-*t*-butyldicarbonate (Boc_2O), gave directly Boc-protected amines (in yields between 71% and 93%). Nevertheless, the methods that rely on catalytic hydrogenation [3] are generally incompatible with the presence, in substrates, of double or triple bonds and of benzyloxycarbonyl and related protecting groups [4]. Not all species able to reduce azides may be mixed with Boc_2O or related reagents (Boc-ON, Boc-N_3, etc.) without causing their decomposition, so that the number of really new one-pot procedures seems limited. In this context, we should draw attention to the work of Afonso [5], who treated azides with Bu_3P and then added Boc_2O at low temperature. Unfortunately, the carbamate yields were generally too low; in fact, for secondary azides and for aromatic azides the method is inappropriate, as competitive reactions take place.

Our long-standing interest in the reaction of phosphazenes (iminophosphoranes) with carboxyl derivatives (RCOX, where X = OH, OCOR, SPy, or SeAr) [6], mainly in connection with the search for new macrolactamisation methods, prompted us to investigate the reaction of phosphazenes with carbonate-like derivatives (ROCOX) such as the Boc-transferring agents. **We report here that the use of trimethylphosphine** (Me_3P, 1.05 equiv) **and 2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile** (Boc-ON, 1.05 equiv) [7], both commercially available, **allowed us to obtain the desired Boc-amines in 87–100% overall yields**. The process, performed in one pot, may be explained as follows:



The results, from the azides, by adding Me_3P first and then Boc-ON, are shown in Table 1 (next page). **By mixing all components together** (azide, 1.1 equiv of Me_3P, and 1.1 equiv of Boc-ON) **in toluene or THF at –20 °C, and stirring at r.t. for 4–5 h, similar yields of Boc-amines (90–100%) were obtained** [8].

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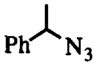
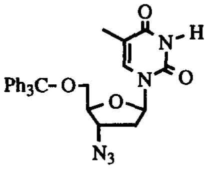
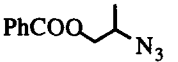
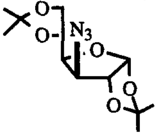
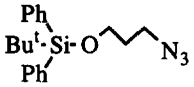
Table 1. Reaction of primary and secondary azides, as well as of phenyl azide, with Me_3P and Boc-ON.[a]

azide	yield of R-NH-Boc	azide	yield of R-NH-Boc	azide	yield of R-NH-Boc
	93%		90%		98%
	100%		90%		
	96%		87%		
	92%			PhN_3	95%

[a] Typical procedure.– To a solution of the organic azide (1 mmol) in toluene (3 mL), under Ar, at r.t., was added Me_3P (1.05 mL of 1 M toluene solution). After ca. 1 h (when no azide was detected by IR or TLC), the flask was cooled to –20 °C and a solution of Boc-ON (259 mg, 1.05 mmol) in toluene (1 mL) was added *via* cannula. After stirring for 5 h at r.t., 50–100 mL of CH_2Cl_2 or Et_2O were added and the solution was extracted with water (×3) and with saturated aq NaCl; the organic phase was dried, concentrated, and filtered through a small pad of alumina (with 99:1 CH_2Cl_2–MeOH as the eluent). Alternatively, washing the above-mentioned dichloromethane or ether solution with 2 M NaOH, drying of the organic layer, evaporation, and purification of the crude product (when necessary) through a short column of silica gel (with CH_2Cl_2–MeOH as above) gave the same results.

To work up the final solution, water was added to hydrolise species of type $RN(PMe_3^+)COOBu^t$ and/or $RN{=}C(OPMe_3^+)OBu^t$ and to extract $Me_3P{=}O$ (which is soluble in H_2O) [9]. The oxime, the other coproduct, may be removed by chromatography or by extraction with aqueous base. Thus, simple separation protocols were sufficient to afford chromatographically and spectroscopically pure Boc-protected amines.

In summary, the improved procedure here reported for the conversion of azides to Boc-amines has significant practical advantages (higher yields and easy workup) over the previous ones based on phosphines and is an alternative to the methods based on catalytic reductions.

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[2] Saito S, Nakajima H, Inaba M, Moriwake T. Tetrahedron Lett. 1989;30:837–838.

[3] Very recently, an azido ester was reduced and protected with H_2, Rh/C, and Boc_2O: Woltering TJ, Weiz-Schmidt G, Wong CH. Tetrahedron Lett. 1996;37:9033–9036.

[4] To overcome this problem, Kotsuki et al. (Kotsuki H, Ohishi T, Araki T. Tetrahedron Lett. 1997;38: 2129–2132) treated azides with Et_3SiH (1.5 equiv), $Pd(OH)_2/C$, and Boc_2O (1.5 equiv), mixing all together in EtOH, to obtain the corresponding Boc-amines in 64–99% yields; although a conjugate double bond survived, in another example a phenolic benzyl group did not.

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[7] Itoh M, Hagiwara D, Kamiya T. Bull Chem. Soc. Jpn. 1977;50:718–721.

[8] Under these conditions phosphatriazene intermediates may be involved (Bosch I, Urpí F, Vilarrasa J. J. Chem. Soc. Chem. Commun. 1995; 91–92).

[9] This is one advantage of Me_3P and Et_3P (Urpí F, Vilarrasa J. Tetrahedron Lett. 1986;27:4623–4624) with regard to Bu_3P and Ph_3P (as $Bu_3P{=}O$ and $Ph_3P{=}O$ cannot be extracted with water from organic solutions). Under the above-mentioned conditions, Bu_3P give similar yields of Boc-amines, but with Ph_3P the reactions are much slower and the yields lie only around 60%.