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# Aqueous phosphoric acid as a mild reagent for deprotection of the *t*-butoxycarbonyl group

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**Abstract**—Aqueous phosphoric acid (85 wt%) is an efficient and mild reagent for the deprotection of *N*-BOC groups. Acid sensitive functionalities including benzyl and methyl esters, TBDMS ether, CBZ and isopropylidene groups are compatible with the reaction conditions. The reactions are high yielding, and the workup is convenient.


Phosphoric acid ($H_3PO_4$) is one of the key raw materials in the chemical industry with the annual output of more than 10 million metric tons in the United States alone.[1] The greatest consumption of pure phosphoric acid is in the production of various salts in the fertilizers, detergents and dentifrice industries. Because pure phosphoric acid is devoid of odor and, when greatly diluted, not injurious to health, it is used for the manufacture of certain foodstuffs such as gelatin and soft drinks.[2,3] Polyphosphoric acid (anhydrous form of phosphoric acid, containing 82–85% $P_2O_5$) is a common reagent in organic synthesis for cyclizations,[4] acylations,[5] alkylations,[6] and Beckmann rearrangments.[7] However, little is known in the literature for the use of phosphoric acid or its aqueous solution in synthetic applications other than its use in dehydrations of 2° and 3° alcohols under heating conditions.[8,9]

We set out to investigate the feasibility of using phosphoric acid to deprotect acid labile protecting groups. Phosphoric acid is a much weaker acid ($pK_{a1}$ 2.15) than $CF_3COOH$ ($pK_a$ 0.3), MsOH ($pK_a$ −0.6), TsOH ($pK_a$ −1.3) and other mineral acids,[10] therefore it is expected to offer advantages for substrates with acid sensitive functionalities other than the protecting group to be deblocked. We chose the *t*-butoxycarbonyl (BOC) group for the initial studies as it is one of the most commonly used protecting groups for amines,[11] and there are many commercially available substrates. Numerous methods have been reported for its deprotection, although most involve the use of strong acids such as $CF_3COOH$, HCl, $H_2SO_4$, TsOH and MsOH or Lewis acids such as $BF_3{\cdot}OEt_2$, TMSI, TMSOTf, $TiCl_4$, $SnCl_4$, $AlCl_3$, $Sn(OTf)_2$, and $ZnBr_2$.[12,13] The deprotection can also be effected with mildly acidic conditions such as Montmorillonite K10 clay catalyst[14] and silica gel (low pressure)[15] or thermolytic cleavage although at a high temperature (150°C). It is also possible to remove the *N*-BOC group in the presence of other acid sensitive functionalities such as *t*-butyl esters and trityl groups (1 M HCl in EtOAc,[16] $H_2SO_4$ in *t*BuOAc or $MeSO_3H$ in *t*-BuOAc/$CH_2Cl_2$[17]). Recently, Yadav et al. reported the deprotection of *t*-butyl esters in the presence *N*-BOC groups by $CeCl_3{\cdot}7H_2O$-NaI.[18]

Table 1 summarizes some examples of BOC group deprotection reactions using aqueous 85 wt% phosphoric acid. The aqueous solution was chosen for economic reasons and ease of handling. The reaction works effectively in removing BOC groups from primary and secondary amines including an imidazole. Benzyl and methyl esters, *t*-butyldimethylsilyl ether, isopropylidene and CBZ groups survive the reaction conditions. Not surprisingly, the aqueous 85 wt% phosphoric acid also deprotects the *t*-butyl ester (entry 8). No racemization was observed for any of the enantiomerically pure substrates as determined by chiral HPLC assays.

In a typical experimental procedure, aqueous phosphoric acid (85 wt%) was added to a solution of the reaction substrate in an organic solvent (THF, acetoni-

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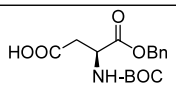
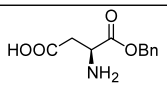
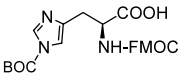
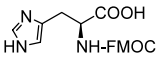
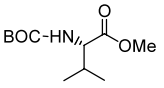
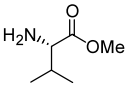
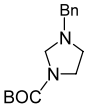
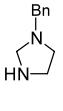
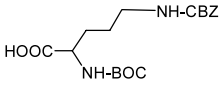
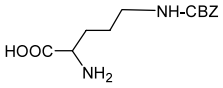
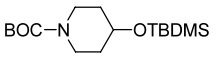
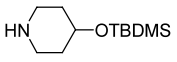
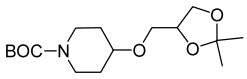
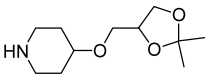
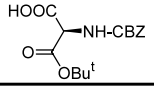
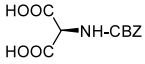
**Table 1.** Deprotection with aqueous phosphoric acid (85 wt%)[21]

| Entry | Substrate | Product | Yield[2] |
|---|---|---|---|
| 1 |  |  | 94% |
| 2 |  |  | 92% |
| 3 |  |  | 97% |
| 4 |  |  | 98% |
| 5 |  |  | 94% |
| 6 |  |  | 94%[3] |
| 7 |  |  | 86%[4] |
| 8 |  |  | 88%[5] |

trile, toluene or methylene chloride). The mixture was stirred at room temperature until reaction was complete (monitored by HPLC, typically 4–8 h). Water was added to dilute the reaction mixture, and sodium hydroxide solution was added to adjust the pH to 7–8. After extractive work-up and removal of solvent, the product obtained was typically >98% purity by HPLC assay without further purification. The reaction was conducted at high concentration, typically with 1 mL of solvent per gram[19] of substrate and 15 equivalents of aqueous phosphoric acid (85 wt%). The reaction proceeded sluggishly (>16 h in some cases) when it was diluted (>5 mL/g substrate) or less amount of the reagent was used.[20] Concentrated aqueous NaOH (50% solution in water) was used in the workup, hence the aqueous layer was fully saturated with sodium phosphate (formed in the pH adjustment), which enhanced the product partition in organic phase. Sodium phosphates formed in the workup also acted as a pH buffer, which effectively prevented the pH of the mixture from going too high in case over charge of the NaOH solution occurred. This feature is advantageous in production settings where use of a pH probe is not readily applicable.

In conclusion, the environmentally benign aqueous phosphoric acid (85 wt%) can be used as an alternate reagent for the deprotection of *N*-BOC groups. The reaction conditions are mild and offer good selectivity among other acid sensitive groups including CBZ, benzyl and methyl esters, TBDMS and isopropylidene groups. The reaction preserves stereochemical integrity of *N*-BOC amino acids. Furthermore, it can be used for *t*-butyl ester deprotection. We are exploring other synthetic applications for the aqueous phosphoric acid, and will report the findings in due course.

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19. For reactions of milligram scales, 0.5 mL of the solvent and 0.5 mL of aqueous 85% $H_3PO_4$ were used.
20. It is possible to heat the reaction to accelerate the reaction to reduce the amount of reagent used when no other acid sensitive functionalities are present. Methyl and benzyl esters, and the isopropylidene group were partially deprotected at 50°C under the reaction conditions.
21. Typical procedure for BOC deprotection: To a solution of 2-*tert*-butoxycarbonylamino-succinic acid 1-benzyl ester (1.0 g, 2.73 mmol) in tetrahydrofuran (1 mL) at room temperature (entry 1, Table 1), was added aqueous phosphoric acid (85 wt%, purchased from Aldrich Chemical Co.) (2.81 mL, 41 mmol) dropwise. The mixture was stirred for 4 h, and HPLC assay showed reaction completion. 5 mL of water was added, and the mixture was cooled to 0°C. 50 wt% NaOH solution was added slowly (Caution: exothermic) to adjust to the pH to ~8. The mixture was then extracted with ethyl acetate (2×20 mL). The combined ethyl acetate phase was dried over magnesium sulfate, concentrated in vacuo to give the desired product as a white solid (0.57 g, 94%). The product showed 98.7% HPLC purity (by area%). It co-eluted with an authentic sample by HPLC.
22. Isolated yields. All products were characterized by NMR and MS. Achiral HPLC analyses were carried out in HP-1100 (Model) using a stable-bond cyano (SB-CN) column (4.6 mm×250 mm) with acetonitrile: 0.2% perchloric acid aqueous buffer (20/80 or 40/60) as mobile phase (2 mL/min) and detection at 210 nm wavelength. Chiral HPLC methods were used for the assays: ChiralPak AD-H column, 4.6×250 mm, hexane:ethanol:diethylamine (90/10/0.2) mobile phase, 1.5 mL/min. 35°C, 210 or 225 nm.
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25. The isolation was simplified by direct dilution with water, followed by extractive workup and isolation using ethyl acetate.