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# AN EXCEPTIONALLY MILD DEPROTECTION OF PHTHALIMIDES

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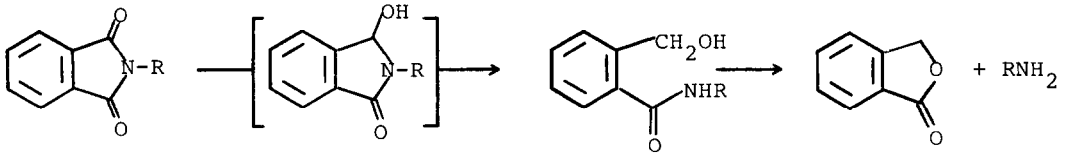
**Summary: Phthalimides are converted to primary amines in an efficient, two-stage, one-flask operation using $NaBH_4$/2-propanol, then acetic acid.**

The development of stable but easily removable amine protecting groups continues to interest both synthetic organic and peptide chemists.[2-5] Particularly in peptide synthesis, the choice of appropriate N-blocking groups is a critical decision if racemization is to be avoided.[6] Sometimes exhaustive substitution of primary amines is desirable to remove both acidic hydrogens, thus modulating nucleophilic character. Phthalimide groups are well-suited to this purpose, but would be more widely employed if deprotection could be achieved without resorting to hydrazinolysis. Because of that shortcoming, other more esoteric blocking groups such as the OX,[7] N,N-diallyl[8] and STABASE[9] derivatives have been recommended as alternatives. We now report a gentle, near-neutral method for removing phthalimide groups that should rekindle interest in these derivatives as practical and versatile amine protecting groups.

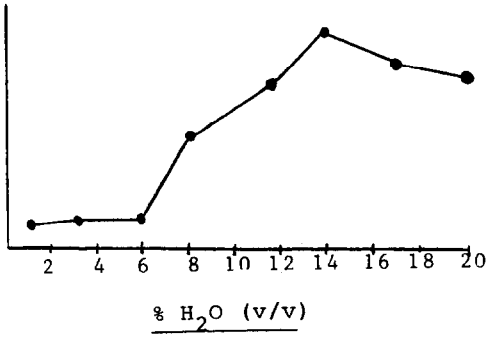



I II III IV

Central to our plan was the conviction that o-hydroxymethyl benzamides like III ought to lactonize rather easily under acidic or basic conditions with concomitant release of the primary amine. The neutral by-product

phthalide (IV), a weakly electrophilic carbonyl compound, should be removable by extractive workup. Since phthalimides undergo extremely facile hydrolysis to phthalamidic acids, we first tried to prepare III by selective hydroboration of those acids. This approach was only marginally successful with N-benzylphthalimide, affording III (R=benzyl) in 40-60% yield. However when III was treated with potassium tert-butoxide, benzylamine and phthalide were released in high yield, underscoring the viability of this strategy.

The partial reduction of I was next examined as a more expedient route to III. Hydride reductions of succinimides can usually be controlled to furnish II,[10] but overreduction often results in both cyclic and acyclic products. In 1961, two papers described the $NaBH_4$ reduction of phthalimides to complex product mixtures in a highly solvent, concentration and workup-dependent process.[11,12] One group detected variable (but always low) yields of phthalide in some reductions.[11] More importantly, Uhle[12] discovered that reductions in aqueous 2-propanol, although slow, formed III in good yield. The Chart below illustrates the effect of varying this solvent mixture to achieve maximal reduction rate. Using 6:1 2-propanol:$H_2O$, we found a wide variety of substituted phthalimides were reduced to III in high yield (24h, rt; see Table). Addition of $ZnCl_2$, $MgCl_2$ or $CoCl_2$ (which forms cobalt boride[13]) had little effect on the rate of reduction, which was even more sluggish with $LiBH_4$. No reduction whatsoever was observed with $NaBH_3CN$.




Cyclization of III to IV with release of the free primary amine was best conducted in aqueous acetic acid (pH 5) for 2h at 80°C.[14] While certain α-amino acids may racemize in glacial acetic acid at reflux,[15] the Table shows that several phthalimide derivatives of such structures were smoothly deprotected

## REDUCTIVE REMOVAL OF PHTHALIMIDES USING SODIUM BOROHYDRIDE

| RNPhth[a] | Product (%Yield) | Rotation | Lit. Rotation[e] |
|---|---|---|---|
| $PhthNCH_2Ph$ | $PhCH_2NH_2$ (81)[c] | --- | --- |
| $PhthN(CH_2)_9CH_3$ | $CH_3(CH_2)_9NH_2$ (88) | --- | --- |
| $PhthN(CH_2)_3CO_2H$ | $NH_2(CH_2)_3CO_2H$ (97) | --- | --- |
| PhthN-L-Phe[f] | L-Phe (70)[d] | -30.9°[e] | -32.5° (c 1.9, $H_2O$) |
| PhthN-L-Glu | L-Glu (95) | +25.7° | +24.9° (c, 1 6N HCl) |
| PhthN-L-Trp | L-Trp (89) | -28.2° | -28.0° (c, 0.5 $H_2O$) |
| PhthN-L-Ala-L-Tyr[b] | L-Ala-L-Tyr (95) | +40.8° | +39.7° (c, 2 $H_2O$) |

(a) Specific rotations of optically active phthalimides, where known, matched reported values.
(b) $[\alpha]_D$ = +59° (c, 1, EtOH).
(c) Controls showed 18% loss during workup due to volatility.
(d) Volatile: controls showed 25% loss during freeze-drying.
(e) Product rotations were obtained at the literature reported concentrations; these rotations all correspond to ammonium salts.
(f) Deprotection of PhthN-L-Phe methyl ester was complicated by some reduction and some hydrolysis of the methyl ester.

**Representative Procedure:** To a stirred solution of N-phthaloyl-4-aminobutyric acid (.200g, .86mmol) in 2-propanol (7.7mL) and $H_2O$ (1.3mL) was added $NaBH_4$ (4.30mmol). After stirring 24h, tlc indicated complete consumption of starting material. Glacial acetic acid (0.9mL) was added carefully and when the foaming subsided, the flask was stoppered and heated to 80°C for 2h. The crude reaction mixture was then eluted onto a Dowex 50 ($H^+$) column (2.7 x10cm), washed with $H_2O$ (150mL), then eluted with 1 M $NH_4OH$ (200mL). Ninhydrin-active fractions were collected and pooled for freeze drying, and thus afforded γ-aminobutyric acid ammonium salt (.100g, 97%).

with no measurable loss of optical activity. In fact, the specific rotation of L-tryptophan was unchanged after 24h exposure to the deprotection conditions. Phthalimides may thus reemerge as useful peptide blocking groups.

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