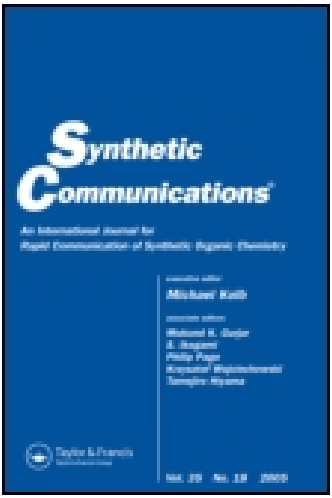


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# A Simple Synthesis of Photolabile α-Methyl Nitrobenzyl Compounds

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# A Simple Synthesis of Photolabile α-Methyl Nitrobenzyl Compounds

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## ABSTRACT

α-Methyl nitrobenzyl compounds have demonstrated superior photochemical release properties when compared to nitrobenzyl compounds lacking α-methyl substitution at the benzylic position. The synthesis of 4-(1-hydroxy-ethyl)-3-nitro-benzoic acid ethyl ester and 4-(1-amino-ethyl)-3-nitro-benzoic acid ethyl ester was each carried out in four steps. The efficient oxidation of 4-ethyl-3-nitro-benzoic acid to 4-acetyl-3-nitro-benzoic acid by 3 mol% chromium trioxide/periodic acid in acetonitrile provides a common, crystallizable precursor from which both hydroxy and amine substituted α-methyl nitrobenzyl compounds may be

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synthesized. This oxidative methodology will be useful in synthesizing a broad array of nitrobenzyl protecting groups.

*Key Words:* Nitrobenzyl compounds; Oxidation; Photolabile protecting groups; α-Methyl groups; Ultraviolet light; Caged compounds; Hemiacetal; Hemiaminal.



## INTRODUCTION

Nitrobenzyl photolabile protecting groups provide a mild, noninvasive means by which small molecules may be photolytically deprotected under a wide variety of solvents and conditions. The versatility of nitrobenzyl groups has encouraged their use as linkers and protecting groups in chemical synthesis as well as biological applications. Polyfunctional nitrobenzyl protecting groups provide the broadest range of potential applications.

In 1975, Rich and Gurawa introduced the 4-(amino-methyl)-3-nitro-benzoic acid class of groups for use as photolabile linkers in solid phase applications, Fig. 1.[1] The compact size of these compounds and the presence of a carboxylic acid group for enhancing water solubility also make variants of these compounds attractive from the standpoint of protecting biologically relevant substrates. Over the last two decades there has been a mounting body of data that suggests nitrobenzyl compounds with methyl groups at the α-benzyl position possess faster rates of release and higher quantum efficiencies of product release.[2] In addition, α-methyl groups result in the formation of a nitroso ketone byproduct, which is intrinsically less reactive than the corresponding nitroso aldehyde. This has the advantage of increasing photolytic yields due to the preservation of released product. Furthermore, the mechanism by which commonly used thiol scavengers react with the α-methyl nitroso ketone has been fully characterized.[3] The suggested mechanism for

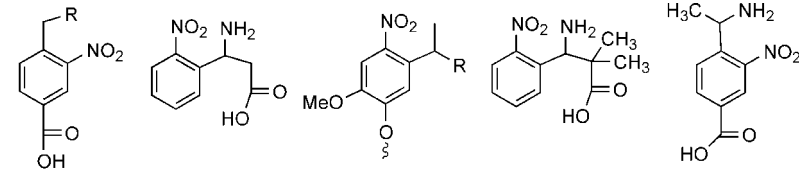



***Figure 1.*** A selection of photolabile protecting groups/linkers.

release of amines, amides, carboxylic acids, alcohols, and phosphates proceeds via the photoinduced formation of hemiacetal or hemiaminal type intermediates that decomposes to release the product and nitroso aromatic group.[4]

Several authors have attempted to improve upon Rich and Gurawa's nitrobenzyl compounds by the incorporation of alkyl groups at the $\alpha$-benzyl position. Photolabile groups incorporating the $\alpha$-methyl nitrobenzyl element have also been developed based upon the 6-nitroveratryl substructure, Fig. 1.[5] A drawback of dimethoxy substitution is that despite greater absorption at longer wavelengths, quantum efficiencies of product release are typically orders of magnitude lower.[6] Furthermore, their absorption extends into the visible spectrum and may complicate their use under standard lighting. Other $\alpha$-alkyl benzyl variants include the 3-amino-3-(2-nitrophenyl)-propionic linker.[7] Although the synthesis of this groups was highly efficient it is prone to undergo acid and base catalyzed beta-elimination, Fig. 1.[8] This prompted the development of the 3-amino-3-(2′-nitrophenyl)-2,2-dimethyl propionic acid protecting group, Fig. 1. The 4-(1-amino-ethyl)-3-nitro-benzoic acid photolabile group is the closest in structure to the first compounds developed by Rich and Gurawa, Fig. 1. The compact size of this compound and stability under basic conditions allowed its efficient use as a water soluble amide protecting group.[9]

## RESULTS

The well established benefits of $\alpha$-benzyl methyl substitution thus prompted the development of a practical, scalable synthesis of $\alpha$-methyl compounds **1** and **2** to serve as needed references in the growing family of nitrobenzyl protecting groups and linkers, Fig. 2. This work demonstrates the first synthesis of **2**.

A frustrating aspect of nitro aromatic compounds is their relative sensitivity to strongly reducing chemistry and organometallic reagents. This limits the means by which substituents may be introduced following nitration. When attempting a highly efficient, scalable synthesis of such compounds introduction of the nitro group should proceed so as to achieve nearly quantitative regioselective conversion to the desired nitro substituted isomer. Originally **1** was synthesized via the coupling of potassium phthalimide with 4-(1-bromo-ethyl)-benzoic acid-ethyl ester in refluxing DMF followed by nitration using fuming nitric acid, $-10^{\circ}C$.[9] The synthesis of **1** was problematic in that it generated an 80 : 20 mixture of ortho : meta isomers that required silica column chromatography. The synthesis of **2** was attempted via nitration of 4-acetyl benzoic acid and 4-(1-acetoxy-ethyl)-benzoic acid using a variety of nitrating conditions. In each case a mixture of isomers or decomposition occurred, Sch. 1.[a]

[a]Nitrating conditions included fuming $HNO_3$ at $-10^{\circ}C$, $HNO_3/H_2SO_4$, $HNO_3/Ac_2O$.

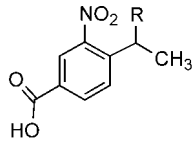
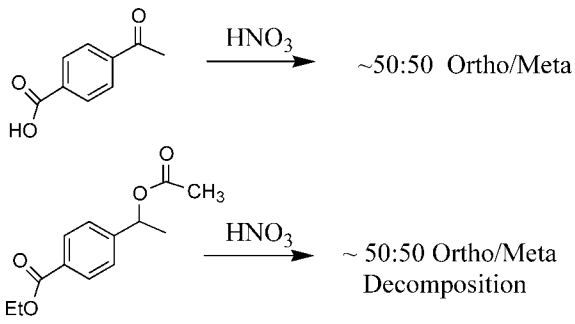



*Figure 2.* **1** = R = $NH_2$, **2** = R = OH.

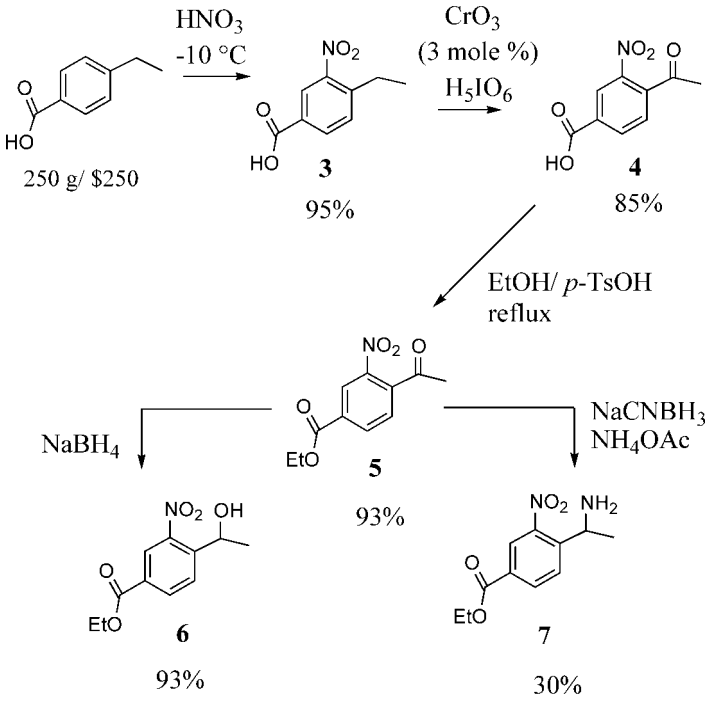


The synthesis of **1** and **2** was thus to follow a route in which the nitro group was introduced first, followed by the oxidative introduction of a ketone which could be easily converted to either the alcohol or amine, Sch. 2. The photolabile groups were to be synthesized as their ethyl ester derivatives to aid in purification and incorporation. The synthesis proceeded via the nitration of commercially available 4-ethyl-benzoic acid using fuming nitric acid at $-10°C$. The presence of strongly directing alkyl and carboxy groups in 4-ethyl-benzoic acid promotes its near quantitative conversion to **3** ($> 95\%$) as a crystalline solid. The selective oxidation of **3** to **4** was carried out using the delightful chromium based chemistry of Yamazaki.[10] The oxidation uses only a catalytic amount of $CrO_3$ (3 mol%) in the presence of an excess of periodic acid, which serves as the terminal oxidant. The reaction proceeds smoothly and cleanly in MeCN to produce ketone **4** in 85% yield as a crystalline solid. This is the first example demonstrating the efficiency of Yamazaki's chemistry in the presence of both *o*-nitro and carboxylic acid groups. Compound **4** was then converted to **5** via *p*-TsOH catalyzed esterfication. Compound **5** may then be used to produce **6** or **7**. Compound **6** was generated via $NaBH_4$ of **5** in 93% yield while reductive amination using $NaCNBH_3/NH_4OAc$ in MeOH produced **7** in 30% yield.

In conclusion, $\alpha$-methyl photolabile protecting groups suitable for protecting both amino and hydroxy containing molecules have been synthesized from a common, inexpensive starting material in good yields.




*Scheme 1.*




*Scheme 2.*

## EXPERIMENTAL SECTION

### General

All $^{1}$H NMR and $^{13}$C NMR were taken on Varian 400 and 500 MHz spectrometers. Mass spectra were taken at Numega Resonance Labs, San Diego, CA. MeCN was HPLC grade (Fisher Scientific). Elemental analysis was carried out by Desert Analytics, Tucson AZ.

### Synthetic Procedures

**4-Ethyl-3-nitro-benzoic acid (3).** Fuming $HNO_3$ (50 mL) was placed in a round-bottomed flask and cooled to $-10^{\circ}$C using a slurry of dry ice/saturated NaCl solution and ice. 4-Acetyl-benzoic acid (10 g, 67 mmol), Fluka, was slowly added over the course of 30 min. After an additional

30 min stirring the reaction was completed. A fritted funnel was placed in a filter flask. Finely crushed ice (200 g) was placed on a fritted funnel and the acid solution poured over it. The ice was vigorously stirred followed by the application of vacuum to the filter flask. The precipitated ice/solid mixture was filtered until the ice had melted. The remaining white solid was then washed with 100 mL of $H_2O$. The solid was dried under vacuum then crystallized from EtOAc/hexane to yield 12.3 g of **3** as white crystals. Yield: 95%. M.p. = 145–146°C. $^1$H NMR (500 MHz, $d_6$-DMSO): $\delta$ 8.26 (d, $J = 1.5$ Hz, 1H), 8.02 (dd, $J = 1.5$ Hz, $J = 8$ Hz, 1H), 7.50 (d, $J = 8.5$ Hz, 1H), 2.78 (q, $J = 15$ Hz, 2H), 1.14 (t, $J = 15$ Hz, 3H). $^{13}$C NMR (500 MHz, $d_6$-DMSO): $\delta$ 165.6, 148.8, 142.7, 133.5, 131.8, 130.2, 125.1, 25.6, 14.5. ESI MS: $m/z$ calcd for $C_9H_9NO_4$ (M−1) = 194, found 194. Anal. Calcd. for $C_9H_9NO_4$ (%): C, 55.38; H, 4.65; N, 7.17; O, 32.79; Found: C, 55.21; H, 4.50.

**4-Acetyl-3-nitro-benzoic acid (4).** Compound **3** (10 g, 51.3 mmol) was added to 44 mL of MeCN. A 0.1 M solution of $CrO_3$ in MeCN was prepared by pulverizing 1 g of $CrO_3$ solid using a mortar and pestle followed by dissolving in 100 mL acetonitrile with the assistance of mild heating (~50°C). Over the course of 3 hr, 15.5 mL of the 0.1 M $CrO_3$/MeCN solution was slowly added along with $H_5IO_6$ (35 g, 154 mmol) accompanied by vigorous stirring. After 12 hr an additional 3.9 mL of 0.1 M $CrO_3$ solution was added along with 11.7 g of $H_5IO_6$. The solution was allowed to stir for an additional 12 hr after which the solvent was decanted and then removed under reduced pressure. The remaining solid was suspended in 500 mL EtOAc and extracted with $H_2O$, then with a 5% sodium thiosulfate solution. The organic layer was dried with $NaSO_4$ and the solvent evaporated. The remaining solid was crystallized using EtOAc/hexane to result in 9.1 g of **4** as pale yellow crystals. Yield: 85%. M.p. = 162°C. $^1$H NMR (500 MHz, $d_6$-DMSO): $\delta$ 8.33 (s, 1H), 8.17 (d, $J = 8$ Hz, 1H), 7.69 (d, $J = 7.5$ Hz), 2.50 (s, 3H). $^{13}$C NMR (500 MHz, $d_6$-DMSO): $\delta$ 199.7, 165.2, 145.8, 140.0, 135, 133.9, 128.7, 125.1, 30.30. ESI MS: $m/z$ calcd for $C_9H_7NO_5$ (M−1) = 208, found 208. Anal. Calcd. for $C_9H_7NO_5$ (%): C, 51.68; H, 3.37; N, 6.70; O, 38.25; Found: C, 51.86; H, 3.56.

**4-Acetyl-3-nitro-benzoic acid ethyl ester (5).** Compound **4** (8.9 g, 42.8 mmol) was added to 250 mL anhydrous EtOH along with *p*-toluenesulfonic acid monohydrate (16.3 g, 85.6 mmol). The solution was refluxed for 4 hr under nitrogen followed by removal of the EtOH under reduced pressure. The remaining solid was dissolved in ethyl acetate then extracted with $H_2O$, then 5% $NaCO_3H$. The organic layer was dried with $NaSO_4$, filtered, and the solvent evaporated to give 9.5 g of **5** as a waxy yellow white solid. Yield: 93%. M.p. = 57–60°C: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.70 (d, $J = 1.6$ Hz, 1H), 8.35 (dd, $J = 1.6$ Hz, $J = 8$ Hz, 1H), 7.49 (d, $J = 8$ Hz, 1 H), 4.45 (q, $J = 7.2$ Hz, 2H), 2.58 (s, 3H), 1.44 (t, $J = 7.2$ Hz, 3H). $^{13}$C

NMR (400 MHz, $CDCl_3$): δ 198.8, 163.4, 145.5, 150.0, 134.8, 132.8, 127.5, 124.2, 62.2, 30.2, 14.3. Anal. Calcd. for $C_{11}H_{11}NO_5$ (%): C, 55.70; H, 4.67; N, 5.90; O, 33.72; Found: C, 55.98; H, 4.62; N, 5.87.

**4-(1-Hydroxy-ethyl)-3-nitro-benzoic acid ethyl ester (6).** Compound **5** (5.0 g, 0.021 mmol) was dissolved in 200 mL of anhydrous EtOH. $NaBH_4$ (0.93 g, 25.2 mmol) was added and the solution heated to 60°C for 90 min. The solvent was then removed under reduced pressure and the remaining solid dissolved in EtOAc, which was then extracted with brine and $H_2O$. The organic layer was dried with $NaSO_4$, filtered, and the solvent removed under reduced pressure to result in 4.65 g of **6** as a waxy white solid. Yield: 93%. M.p. = 51–53°C: $^1$H NMR (500 MHz, $CDCl_3$): δ 8.58 (d, $J = 1.5$ Hz, 1H), 8.28 (dd, $J = 8.5$ Hz, 1H), 7.96 (d, $J = 8$ Hz, 1H), 5.48 (q, $J = 6$ Hz, 1H), 4.42 (q, $J = 7.5$ Hz, 2H), 1.58 (d, $J = 6$ Hz, 3H), 1.42 (t, 3 H, $J = 7$ Hz): $^{13}$C NMR (500 MHz, $CDCl_3$): δ 164.4, 147.5, 145.6, 134.0, 130.6, 128.0, 125.4, 65.7, 63.1, 24.7, 14.5. ESI MS: $m/z$ calcd for $C_{11}H_{13}NO_5$ (M − 1) = 238, found 238. Anal. Calcd. for $C_{11}H_{12}NO_5$ (%): C, 55.46; H, 5.08; N, 5.88; O, 33.58; Found: C, 54.90; H, 5.15; N, 6.02.

**4-(1-Amino-ethyl)-3-nitro-benzoic acid ethyl ester (7).** Compound **5** (4 g, 16.9 mmol) was dissolved in 160 mL of anhydrous MeOH. Ammonium acetate (19.5 g, 0.25 mmol), >99.9% Aldrich, was added followed by $NaCNBH_3$ (4.7 g, 76 mmol). The solution was refluxed under nitrogen for 7 hr followed by cooling and addition of 340 mL of 0.5 M $NaHCO_3$. The solution was then stirred for 24 hr followed by acidification to pH ∼3 using an aqueous 5% HCl solution. The solution was then extracted with $CHCl_3$, the aqueous layer separated and brought to ∼ pH 8.0 with 0.5 M $NaHCO_3$. The solution was then extracted 3 × with chloroform. The chloroform layer was dried with $NaSO_4$, filtered, and the solvent evaporated to result in 1.22 g of **7** as a light yellow oil. Yield: 30% $^1$H NMR (500 MHz, $CDCl_3$): δ 8.42 (d, $J = 2.0$ Hz, 1H), 8.24 (dd, $J = 8.5$ Hz, 1H), 7.92 (d, $J = 8$ Hz, 1H), 4.65 (q, $J = 6.5$ Hz, 1H), 4.42 (q, $J = 7.0$ Hz, 2H), 1.87 (2H), 1.47 (d, $J = 6.5$ Hz, 3H), 1.41 (t, 3 H, $J = 7$ Hz). Anal. Calcd. for $C_{11}H_{14}N_2O_4$ (%): C, 55.46; H, 5.92; N, 11.76; O, 26.86; Found: C, 54.44; H, 6.03; N, 11.37.

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