

Synthesis of *N*-Benzylated Anilines from the Reaction of Anilines and Benzyl Chloroformate

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ABSTRACT

Reactions of benzyl chloroformate with a series of substituted anilines produced *N*-carbobenzyloxy “CBZ” products along with the unexpected *N*-benzylated “Bn” compounds. Reaction of aniline, **1a**, gave the CBZ, or **2a**, and Bn, or **3a**, products in 29% and 14% yield, respectively. For 2-nitro-, 2-bromo-, and 2-bromo-5-nitroanilines, the *N*-benzylated compounds were produced exclusively. However, 2-methoxy-, 4-bromo-, 4-iodo-, and 4-ethylanilines gave mainly CBZ products. Other compounds reported in this study gave mixtures of the two products. For 4-chloro-3-nitroaniline, in addition to the Bn and CBZ products (53% and 14% yield, respectively), a *N,N*-dibenzylated product was isolated in 27% yield. Collectively, the results indicated that electron-withdrawing groups, particularly at the *ortho* position, directed the formation of Bn compounds, whilst electron-donating groups, especially at the *ortho* and *para* positions, favored the synthesis of CBZ products.

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Synthetic transformations involving amines are important in organic chemistry. This is partly due to their high nucleophilicity and basicity, as well as their common occurrence in natural products. Consequently, a wide number of methods have been developed to selectively protect amino groups.^[1] The carbobenzyloxy carbamate or “CBZ” moiety is an example of such protecting groups. Owing to its ease in preparation and removal, the CBZ group is widely used in the synthesis of natural products.^[2] Despite its versatility for use with aliphatic amines, such as protection of the amine functionality in amino acids, its usage with aromatic amines, anilines, is less common.^[1] In July 2003, a search using SciFinder Scholar for preparation of CBZ protected anilines produced very few “hits.”^[3] In one specific example, the reaction of aniline (**1a**) with benzyl chloroformate, conducted in the presence of lithium hydroxide and aluminum oxide, gave the CBZ protected aniline product (**2a**) in 95% yield.^[3a]

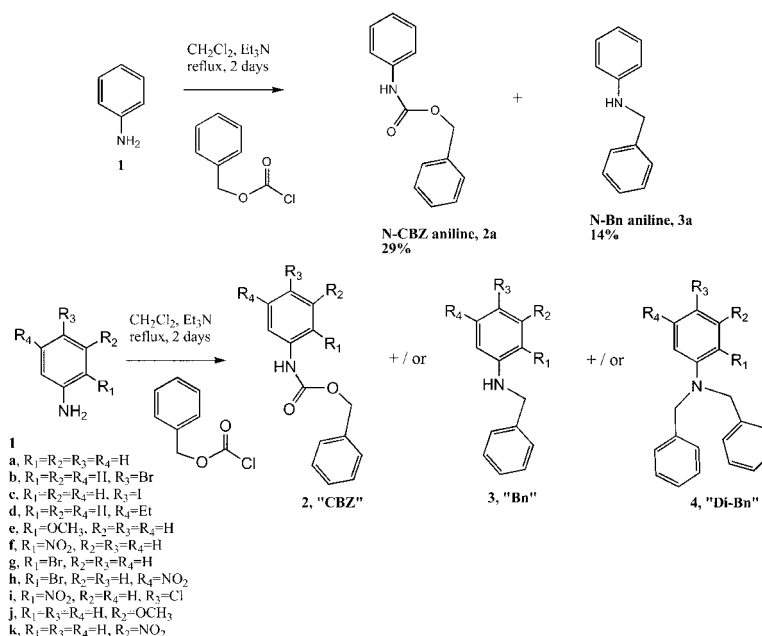
As part of our on-going studies toward the synthesis of analogs of the natural products CC-1065^[4] and the duocarmycins,^[5] we had to protect aromatic amine functionalities on many occasions. In some cases the *N*-BOC (*tert*-butoxycarbonyl)^[6] or *N*-Bn (benzyl)^[7] groups were used, but, there instances where a CBZ group was preferred. In our hands, the reaction of aniline (**1a**) with benzyl chloroformate in refluxing methylene chloride and in the presence of triethylamine did not give a high yield of the desired CBZ product **2a** (29% isolated yield). Moreover, a significant amount of an unexpected *N*-benzyl product **3a** was isolated in 14% yield. From this initial discovery, we undertook a systematic study to evaluate the structure and reactivity of a series of anilines with benzyl chloroformate. The anilines were grouped into three categories. They either contained electron-withdrawing groups at the *ortho* and/or *para* position(s), electron-donating groups in the *ortho* or *para* position, and either an electron-donating or electron-withdrawing group at the *meta* position. The results obtained from the studies were interesting because anilines that contained electron-withdrawing groups at the *ortho* position gave, in some cases, exclusively the *N*-benzyl products, making these reactions synthetically viable. Conversely, anilines containing electron-donating groups produced mainly *N*-CBZ compounds, again in high yields making these reactions synthetically useful.

The general synthetic scheme for the reaction of the substituted anilines with benzyl chloroformate is given in Sch. 1. For a typical reaction, the aniline was dissolved in methylene chloride that had been dried over molecular sieves 3 Å, and the solution was chilled in an ice bath. To this solution was added



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Scheme 1. Reaction of anilines **1a–k** with benzyl chloroformate.

three mole equivalents of triethylamine, also dried over molecular sieves 3 Å. This solution was placed in an ice bath, and while stirring under a drying tube (drierite), a solution of 6 mol equivalents of benzyl chloroformate in dry methylene chloride was added in a dropwise manner. After the addition was completed, the reaction mixture was warmed to room temperature then heated to reflux for 2 days. Upon work-up, the organic extract was purified by silica gel chromatography, and the products were characterized by 500 MHz ^1H NMR, FT-IR and mass spectrometry. A summary of representative spectral characteristics for the compounds described in this study is given in Table 1. For the case of aniline, the structures of the *N*-CBZ and *N*-benzyl aniline products were unambiguously determined by comparison of their spectral data to literature values.^[3,8] In all cases, the benzylic CH_2 signals for the *N*-CBZ and *N*-Bn compounds resonate at characteristic chemical shifts in the ^1H NMR spectra. For *N*-CBZ the signal is typically located at about 5.2 ppm, but, for *N*-Bn the resonance is situated around 4.3–4.7 ppm.

The results from the coupling of eleven different anilines to benzyl chloroformate are given in Table 2. The results are divided into three categories according to the electronic properties and position of the substituent.



Table 1. Spectral characteristics for the compounds reported in this article.

Compound	IR C=O (cm ⁻¹)	¹ H NMR (CDCl ₃) ppm ^a	MS (EI) M ⁺
2b	1701	5.20	306
3b	—	4.68	262
2c	1698	5.20	353
3c	—	4.64	309
2d	1702	5.21	255
3d	—	4.65	211
2e	1701	5.25	257
3f	—	4.56	228
3g	—	4.65	262
3h	—	4.48	307
2i	1708	5.21	307
3i	—	4.34	263
4i	—	4.68	353
2j	1709	5.21	257
3j	—	4.61	213
2k	—	4.73	228
3k	1707	5.20	272

^aChemical shift of the benzylic protons.

Aniline (**1a**) was studied as a reference compound, and for comparison to a literature report.^[3] The results indicate that anilines containing an electron-donating group at either the *para* or *ortho* position favor the formation of *N*-CBZ products (**2b–e**), particularly for 2-methoxyaniline, where the product **2e** was isolated exclusively in 98% yield. Electron-donating properties apparently play a role in promoting the synthesis of the *N*-CBZ product, presumably by enhancing the electron density on the amino function through resonance effects. This contention is supported by evidence that reaction of 3-methoxyaniline (**1j**), which has limited through resonance effects, with benzyl chloroformate gave the *N*-CBZ (**2j**) and *N*-Bn (**3j**) materials in almost equal proportions.

For anilines (**1f–i**), which contain electron-withdrawing groups, the results were generally opposite to those observed for reactants **1a–e**. There was a preponderance amount of *N*-benzyl products, and in several cases (**1f–h**), no *N*-CBZ products was isolated. It is worthy to note that reactions of **1f–h** gave the corresponding *N*-Bn compounds (**3f–h**) in 58–91% yields. Reaction of 4-chloro-2-nitroaniline (**1i**) gave mainly *N*-benzyl products, which was expected. But, in addition to the *N*-Bn product (**3i**), a *N,N*-DiBn (dibenzylated) compound (**4i**) was isolated and characterized. In the final entry, 3-nitroaniline also reacted to give the *N*-Bn product **3k**, but the main



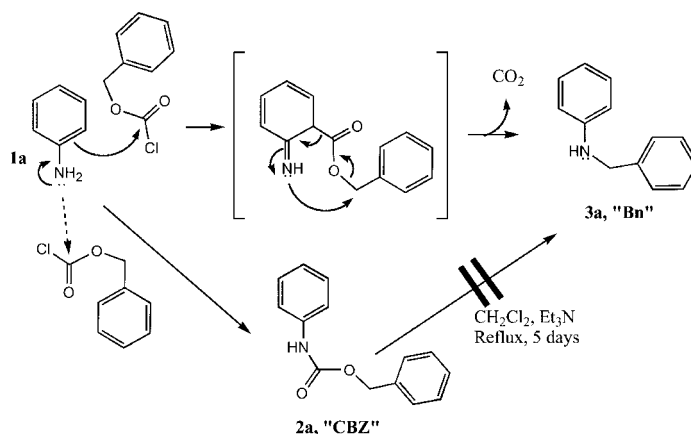
Table 2. Percent yields from the reaction of eleven different anilines with benzyl chloroformate. The yields are reported for products that had been purified by silica gel column chromatography.

Anilines 1	"CBZ" compounds 2	"Bn" compounds 3	"Di-Bn" compounds 4
a , R ₁ = R ₂ = R ₃ = R ₄ = H	29	14	0
<i>Electron donating groups</i>			
b , R ₁ = R ₂ = R ₄ = H, R ₃ = Br	48	1	0
c , R ₁ = R ₂ = R ₄ = H, R ₃ = I	38	2	0
d , R ₁ = R ₂ = R ₄ = H, R ₃ = Et	25	0	0
e , R ₂ = R ₃ = R ₄ = H, R ₁ = OCH ₃	93	0	0
<i>Electron withdrawing groups</i>			
f , R ₂ = R ₃ = R ₄ = H, R ₁ = NO ₂	0	91	0
g , R ₂ = R ₃ = R ₄ = H, R ₁ = Br	0	70	0
h , R ₂ = R ₃ = H, R ₁ = Br, R ₄ = NO ₂	0	58	0
i , R ₂ = R ₄ = H, R ₃ = Cl, R ₁ = NO ₂	14	53	27
<i>Meta-substituted anilines</i>			
j , R ₁ = R ₃ = R ₄ = H, R ₂ = OCH ₃	42	38	0
k , R ₁ = R ₃ = R ₄ = H, R ₂ = NO ₂	39	12	0

product was *N*-CBZ **2k**. From these experiments, the data suggest that electron-withdrawing moieties at positions *ortho* and *para* to the amino group promote *N*-benzylation, presumably through resonance effects.

Since the synthesis of *N*-benzyl products from reactions of anilines and benzyl chloroformate is unprecedented, further studies were conducted to explain their formation. In an attempt to investigate whether the *N*-Bn compounds were produced from rearrangement and decarboxylation of the CBZ compounds, a solution of *N*-CBZ aniline **2a** in methylene chloride and triethylamine was heated to reflux and monitored for 5 days. At the end of the reaction the *N*-CBZ compound **2a** remained unchanged, thus indicating that the formation of the *N*-Bn compound **3a** did not come from **2a**. Based on the available information, it is reasonable to suggest that formation of the *N*-Bn compounds might be a result of Freidel–Crafts acylation, followed by rearrangement and a concomitant loss of carbon dioxide. As indicated in Sch. 2, an electron-withdrawing group would pull electron density away from the amino group. That, in turn, would reduce the nucleophilicity of the amine, increase the electron density in the phenyl moiety, and facilitate the Freidel–Crafts reaction. The resulting imine intermediate would rearrange and eliminates carbon dioxide to produce the *N*-Bn compound **3a**.





Scheme 2. A proposed mechanism for the formation of the *N*-Bn compounds.

In conclusion, this article describes an unexpected discovery of substituent effects on the reaction of anilines with benzyl chloroformate. Depending on the electronic properties of the substituent(s), either the *N*-CBZ or *N*-Bn products could be produced in high chemical yields.

EXPERIMENTAL

A Representative Procedure for the Reaction of Aniline with Benzyl Chloroformate

A solution of aniline **1a** (500 mg, 5.34 mmol) in dry CH_2Cl_2 (15 mL) and containing dry triethylamine (2.2 mL, 16 mmol) was chilled in an ice-bath. While the solution was stirred, a solution of benzyl chloroformate (4.6 mL, 32 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise through a self-equalizing funnel, which had an attached drying tube containing drierite. After 15 min, the reaction mixture was warmed to room temperature, the dropping funnel was replaced with a reflux condenser, and the solution was heated to reflux for 2 days. The reaction mixture was cooled to room temperature then poured into 1 M HCl, and the organic materials were extracted with CH_2Cl_2 (50 mL), then washed with saturated Na_2CO_3 and dried over Na_2SO_4 . Removal of the drying agent and solvent gave a semi solid that was purified by silica gel column chromatography, using 5% EtOAc-petroleum ether as a solvent. The less polar *N*-Bn product (**3a**) was isolated as a viscous colorless oil (137 mg, 14%), and the *N*-CBZ compound was isolated as a white solid



(352 mg, 29%). *N*-Bn (**3a**): IR (neat) 3087, 3018 2910, 1597, 1503, 1449, 1356, 1201, 748, 729, 695; ¹H-NMR (CDCl₃) 7.33 (t, 8.0, 2H), 7.26 (m, 3H), 7.17 (t, 8.0, 2H), 6.75 (d, 8.0, 2H), 6.70 (t, 8.0, 1H), 4.66 (s, 2H); MS (EI) 183 (M⁺, 25%). *N*-CBZ (**2a**): M.p. 68°C; IR (neat) 3323, 3146, 3058, 3028, 2950, 1709, 1601, 1538, 1445, 1314, 1220, 1054, 754, 695; ¹H NMR (CDCl₃) 7.20–7.45 (m, 9H), 7.08 (t, 8.0, 1H), 6.76 (s br, 1H), 5.25 (s, 2H); MS (EI) 223 (M⁺, 35%).

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