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The reaction of *o*-amino aryl carboxylic acids with Grignard reagents. The unusual effect of the *N*-protecting group on aryl ketone formation†

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Abstract—The addition of Grignard reagents to the *o*-amino aryl carboxylic acids without any additive forms the tertiary carbinol as a major product. Unexpectedly, the aryl ketones are formed as the only isolated product if *o*-amino moiety of anthranilic acids is protected with Boc, trifluoroacetyl, and pivaloyl protecting groups.

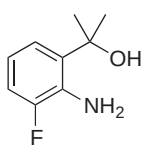
The reaction of a Grignard reagent with a carboxylic acid is not a practical approach for synthesising ketones. Often, the reaction is plagued by low yield of ketones and the formation of tertiary alcohols.[1–3] Solutions to this problem have involved the addition of a Grignard reagent to carboxylic acid derivatives such as Weinreb amides and acyl hemiacetals.[4] Other methods to prevent the formation of alcohols include the use of a pre-formed lithium carboxylate or a nickel catalyst.[5–7] Although the above methods are well documented, the direct addition of Grignard reagents to carboxylic acids to form ketones is an area which has been largely unsuccessful.

During our research, an expedient synthesis of carbinol **1** from anthranilic acids was sought. To this end, methylmagnesium bromide was reacted with the 3-fluoroanthranilic acid to yield the desired carbinol **1** in good yield. Surprisingly, when the amino group of 3-fluoroanthranilic acid was protected with Boc group and treated with the methyl Grignard reagent, ketone **2** was formed in high yield instead of the expected tertiary carbinol **3**.

Apparently, the formation of ketone **2** was mediated by the Boc protecting group. We have examined a number of *N*-protected anthranilic acids as well as various Grignard reagents in this reaction and now wish to report that such a transformation is general in scope among the reactions we examined.

The protecting groups employed in the study included Boc, pivaloyl and trifluoroacetyl groups. The *N*-protected starting materials can be readily prepared from corresponding anthranilic acids following literature procedures.[8]

The various substrates and a number of Grignard reagents were examined as illustrated in Tables 1 and 2. The results are given as the isolated yield of the product.[9] The only other material isolated from the reactions was starting material.



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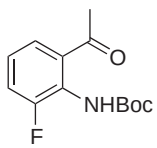

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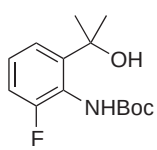

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Keywords: ketone formation; Grignard reagents; protecting groups.

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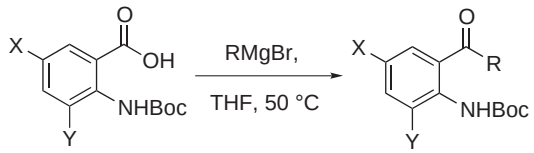
Table 1. Boc mediated ketone formation

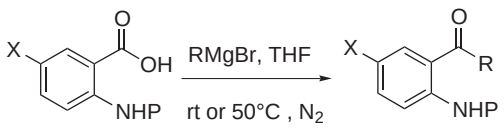


4 **5**

Entry	RMgBr	X	Y	Yield (%) of **5**
1	Methyl	H	H	<5
2	Methyl	H	F	80 (82)[a]
3	Methyl	F	H	66
4	Isopropyl	H	F	89
5	Phenyl	H	F	29
6	Phenyl	F	H	27
7	Vinyl	H	F	27

[a] Yield in parenthesis was obtained by following the procedure of Ref. 5.

Table 2. Pivaloyl and trifluoroacetyl mediated ketone formation



6 **7**

Entry	P	X	R	Yield (%) of **7**
8	*t*-BuCO	H	Me	52 (50)[a]
9	*t*-BuCO	H	Ph	40
10	*t*-BuCO	Br	Me	70
11	*t*-BuCO	Br	Ph	50
12	CF_3CO	H	Me	50
13	CF_3CO	Br	Me	65

[a] Yield in parenthesis was obtained by following the procedure of Ref. 5.

As illustrated in Tables 1 and 2, aryl ketones were formed mostly in good yield from the reaction of Grignard reagents and three different *N*-protected anthranilic acids. For the unsubstituted *N*-protected anthranilic acids, the amide protecting groups worked better than Boc and gave higher yields of ketone products (about 50% yield of ketones formed for pivaloyl and trifluoroacetyl, entries 8 and 12 vs <5% for Boc, entry 1). The aryl substituent (X or Y) significantly affected the reactivity of the *N*-protected anthranilic acids with Grignard reagents. Electron withdrawing halogen moieties increased the formation of ketones presumably because it increased the electrophilicity of the carboxylic acid group. This finding was more evident for the Boc protecting group as demonstrated by the first three examples in Table 1. The unsubstituted Boc protected anthranilic acid only gave a trace amount of ketone (entry 1) while its fluoro substituted congeners afforded ketones in over 60% yield (entries 2 and 3).

Among the Grignard reagents examined, aliphatic Grignard reagents gave higher yields than did the vinyl or aryl species (entries 2–4 vs 5–7). This result was not surprising since the alkyl anions are considered to be more nucleophilic than aryl or vinyl anions.

Diethyl ether was also examined as a solvent and found to be less desirable than THF as the reaction in diethyl ether was slower and not as clean. To examine if esters of *N*-protected *o*-amino aryl carboxylic acids form aryl ketones when reacted with Grignard reagents, *N*-Boc methyl anthranilate (methyl ester of entry 1) was treated with methylmagnesium bromide and the carbinol was formed in quantitative yield instead of aryl ketone.

Using a pre-formed lithium carboxylate[5] compared to the free *N*-protected anthranilic acid used in this study offered no advantage. Comparable yields of aryl ketones were obtained as illustrated from entries 2 and 8 of Tables 1 and 2. It has also been shown that the 2-tetrahydrofuranyl acyl hemiacetal ester[4] of carboxylic acids is converted to the ketone upon treatment with Grignard reagents. When the carboxylic acid moiety of **6** (P = *t*-BuCO, X = H) was converted into its 2-tetrahydrofuranyl acyl hemiactetal ester[4] and treated with methyl Grignard reagent carbinol instead of ketone was obtained as a major product.

In conclusion, an unusual reaction for the formation of ketones directly from the *N*-protected anthranilic acids and Grignard reagents was unveiled. This novel finding provided an interesting insight into the effect of the *N*-protecting group on the reaction outcome and represents another useful way to prepare *o*-amino aryl ketones since the starting materials are readily available and the *N*-protecting groups can be easily removed.[8] Furthermore, *o*-amino aryl ketones are extremely useful intermediates in the synthesis of a variety of the heterocyclic ring systems, for example, benzodiazepines.[10]

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9. General procedure for synthesis of aryl ketones. A solution of the *N*-protected anthranilic acid in anhydrous tetrahydrofuran at 0°C under nitrogen was treated with an etheral solution of Grignard reagent (5 equivalents). After addition, the mixture was either warmed to room temperature or heated to 50°C overnight. The reaction solution was then poured onto ice, the pH adjusted to 5–7, and extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, and concentrated. The residue was purified via a silica gel flash chromatography to afford the desired ketone. All products have been characterised (^{1}H NMR, MS, CHN).
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