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# A DIRECT SYNTHESIS OF PRIMARY AMIDES FROM GRIGNARD REAGENTS

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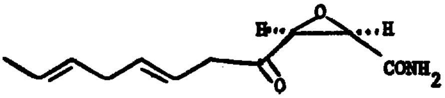
In a preliminary investigation of approaches to the total synthesis of cerulenin (1)[2] and related compounds, we wished to convert the terminal acetylene 2 to the acetylenic primary amide 3.[3]



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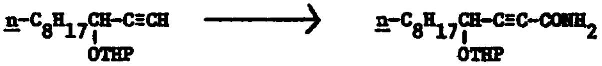


$\underline{n}\text{-}C_8H_{17}\underset{\text{OTHP}}{\underset{|}{CH}}\text{-}C{\equiv}CH \longrightarrow \underline{n}\text{-}C_8H_{17}\underset{\text{OTHP}}{\underset{|}{CH}}\text{-}C{\equiv}C\text{-}CONH_2$

2 3

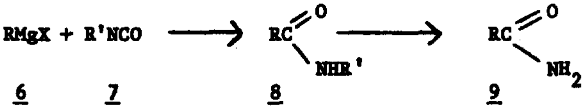
No simple method for achieving a conversion of the type $RC{\equiv}CH \rightarrow RC{\equiv}C\text{-}CONH_2$ is known. A sequence which requires the intermediacy of the acid chloride 4 is incompatible with the presence of the tetrahydropyranyl ether protecting group.[4a] An alternative method, the ammonolysis of the methyl ester 5 in a solution composed of 50% liquid ammonia and 50% ethylene glycol and containing a trace of $NH_4Cl$ requires 10 hours even at 75°.[4b]

$RC{\equiv}C\text{-}COCl$ $R\text{-}C{\equiv}C\text{-}CO_2CH_3$

4 5

Therefore we sought a more facile and general method of accomplishing a one-carbon homologation which would afford a primary amide. Secondary amides (8) may be conveniently prepared by treatment of a covalent isocyanate (7) with a Grignard reagent 6.[5] If the nature of the isocyanate substituent R' were such that it could easily be removed from the nitrogen in amide 8, this

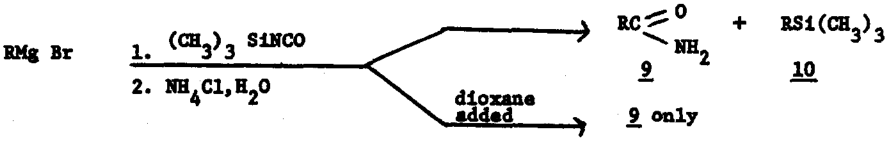
Grignard synthesis would afford primary amides as well as secondary amides. We have found that trimethylsilyl isocyanate (7a)[6] and chloroacetyl isocyanate (7b)[7] are particularly suited to this approach to primary amides, that the transformation is general for aromatic and aliphatic as well as acetylenic Grignard reagents, and that in the reaction with trimethylsilyl isocyanate, the conversion 6 → 9 requires only one step.



a. R' = $Si(CH_3)3$

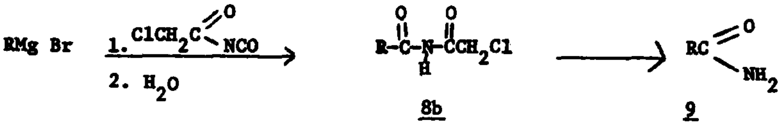
b. R' = $COCH_2Cl$

The addition of trimethylsilyl isocyanate to a solution of Grignard reagent, followed by aqueous workup, afforded the amide 9 along with varying amounts of the substituted silane 10.[7] The product distribution in this reaction was found to be solvent dependent. The presence of dioxane greatly increased the addition reaction (6 → 9), to the exclusion of the substitution reaction (6 → 10). No silanes could be detected in mixtures from these experiments and the amides could be isolated directly.



In a typical procedure, a 0.9 M solution of the Grignard reagent was prepared in ether or tetrahydrofuran and added to a slight excess of trimethylsilyl isocyanate in 3 - 5 volumes of dioxane. The reaction mixture was stirred at 85-95° for 2 - 2½ hours, allowed to cool to room temperature, and quenched with aqueous ammonium chloride. The product was isolated from chloroform/ether and recrystallized. Specific results are recorded in the Table.

In the case of the reaction of a Grignard reagent with chloroacetyl isocyanate, the initially isolated product is the imide 8b. Hydrolytic or reductive removal of the chloroacetyl group affords the unsubstituted amide 9. Experimental procedures for each of these transformations follow.



A 0.9 M solution of the Grignard reagent was prepared in tetrahydrofuran and was slowly added to a slight excess of chloroacetyl isocyanate in 2 - 3 volumes of tetrahydrofuran at -70°. After stirring for 5 - 10 minutes at -70°, the cold bath was removed and when the reaction mixture reached -30°, it was quenched with saturated ammonium chloride solution. The intermediate imide 8b was isolated from chloroform/ether and recrystallized (see Table).

A sample of imide 8b was treated with 1.5 equivalents of sodium hydroxide in methanol. Thin layer chromatography indicated that the reaction was complete in a few minutes. The amide 9 was isolated from chloroform/ether and recrystallized (see Table).

Alternatively, excess zinc dust was added to a methanol solution of imide 8b. After 1½ hours, the reaction mixture was filtered and partitioned between chloroform/ether and water. Amide 9 was isolated and recrystallized (see Table).

Table - The Reactions of Grignard Reagents with Substituted Isocyanates:[a]

Yields and Melting Points of Products

| R | 9[b] (from 2a) | 8[b] | 9[c] (from 8b by hydrolysis) | 9[c] (from 8b by reduction) |
|---|---|---|---|---|
| $C_6H_5$- | 49%<br>125.5° | 56%<br>157.5-158.5° | 52%<br>126.5-128° | 82%<br>127-128° |
| $C_6H_5C{\equiv}C$- | 48%<br>106.5-107° | 76%<br>145.5-147.5° | 83%<br>107.5-108.5° | 90%<br>102.5-104.5° |
| n-$C_7H_{15}$- | —— | 84%<br>106.5-107.5° | 67%<br>104.5-105.5° | 86%<br>100.5-102° |
| $C_6H_5CH_2CH_2CH_2$ | 50%<br>81.5-83.5° | —— | —— | —— |

a. All crude yields are greater than 70%. Crude products were recrystallized from benzene/hexane. All products have ir and nmr spectra consistent with the assigned structures. b. Yields are based on $C_6H_5Br$, $C_6H_5C{\equiv}CH$, n-$C_7H_{15}Br$, and $C_6H_5CH_2CH_2CH_2Br$, respectively. c. Yields are based on the corresponding imide 8b.

This method complements the previously known 1-carbon homologations of Grignard reagents.[9] Efforts are underway to apply this method to the synthesis of cerulenin and other functionalized amides.

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6. The procedure of G. S. Forbes and H. H. Anderson, J. Amer. Chem. Soc., 70, 1222 (1948), was modified. Xylene was used as a solvent and the product mixture was fractionally distilled.

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