

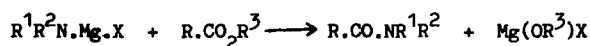
AMIDE FORMATION WITH AMINOMAGNESIUM COMPOUNDS

R. P. Houghton and C. S. Williams

Department of Chemistry, University College,  
(University of Wales), Cathays Park, Cardiff.

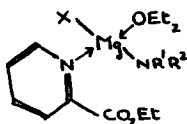
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Treatment of a primary or secondary amine with one equivalent of a methyl magnesium halide affords a compound of the type  $R^1R^2N.MgX$  which reacts with carboxylic esters to give amides:



This reaction, the Bodroux reaction (1), has not been extensively used for the preparation of amides, probably because of the comparatively poor yields which are usually obtained, *cf.* ref.

(2). We have found, however, that with ethyl picolinate and other esters in which the ester group is adjacent to a functional group which can co-ordinate with magnesium the yields of amides are very high when a non-co-ordinating solvent is used. We consider that the reaction with such esters proceeds at least partly through complexes, *e.g.* (I), in which the



(I)

nucleophilic nitrogen atom of the amine residue is held close to the ester group. The alternative possibility that the ester group is activated by co-ordination with the magnesium appears to be ruled out by a study (3) of the Bodroux reaction with Schiff bases of glycine ethyl ester.

In a typical experiment ethyl picolinate (2.38 g.) was added to the aminomagnesium compound prepared from di-*n*-butylamine (2.14 g.) and methyl magnesium iodide (from methyl iodide, 2.35 g.) in benzene (50 ml.). The mixture was refluxed for 4 hr. and then decomposed by the addition of water to give *N,N*-di-*n*-butylpicolinamide (89%).

To compare the reactivities of various ethyl esters in the Bodroux reaction, benzylaminomagnesium iodide was used as the aminomagnesium compound with refluxing benzene as

the solvent. The yields of benzylamides obtained after a reaction time of 1 hr. are given in Table 1. It can be seen that esters which would be expected to form complexes

TABLE 1.

Ethyl Ester	Yield (%) of Benzylamide	
Methoxyacetate	92	43*
Picolinate	69	50*
2'-Pyridylacetate	55	
Thiomethoxyacetate	40	
<u>iso</u> -Nicotinate	26	32*
Benzoate	17	28*

\*With 1,2-dimethoxyethane as the solvent

analogous to (I) gave substantially higher yields than esters which could not form complexes of this type. It is noteworthy that when 1,2-dimethoxyethane was used as the solvent instead of benzene the yields of benzylamides obtained from ethyl methoxyacetate and ethyl picolinate were lowered, but the yields obtained from ethyl benzoate and ethyl iso-nicotinate were raised. This suggests that a co-ordinating solvent increases the nucleophilicity of the nitrogen atom of an aminomagnesium compound, but inhibits the formation of complexes of type (I) by competing with the ester for the magnesium. The former effect is analogous to the increase in the nucleophilicity of the alkyl groups of lithium, magnesium and aluminium alkyls which arises when 1,2-dimethoxyethane is used as the solvent for these compounds (4).

In order to use aminomagnesium compounds in the preparation of  $\alpha$ -amino amides from the ethyl esters of  $\alpha$ -amino acids, the amine was added to an ether/dioxan solution of diethyl magnesium to give the amino(ethyl)magnesium compound (Et.Mg.NHR). This was treated with the Schiff base (1 mol.) formed from the  $\alpha$ -amino ester and either 1-phenylpropan-1,3-dione or pentan-2,4-dione, and the resultant complex [formulated as (IIa) or (IIb)] was refluxed for 1-4 hr. in benzene to give the Schiff base (III) of the  $\alpha$ -amino amide (see Table 2). The parent  $\alpha$ -amino amide was obtained by hydrolysis of the Schiff base with hydrochloric acid, or by treatment with bromine water (5). As expected, the amino amides obtained from optically active amino esters were completely racemic.

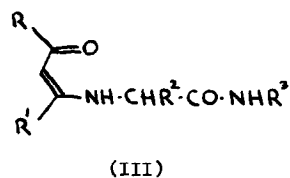
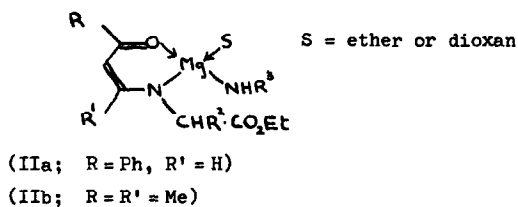


TABLE 2.

Yields of Schiff Bases (III) of  $\alpha$ -Amino Amides.

R	Schiff Base (III)			Yield (%)
	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	
Me	Me	H	CH <sub>2</sub> Ph	69
Ph	H	H	CH <sub>2</sub> Ph	87
Me	Me	Me	CH <sub>2</sub> Ph	60
Me	Me	CH <sub>2</sub> Ph	CH <sub>2</sub> Ph	46
Ph	H	CH <sub>2</sub> Ph	CH <sub>2</sub> Ph	69
Me	Me	H	Ph	62
Me	Me	Me	Ph	49
Me	Me	H	n-Bu	59
Me	Me	Me	n-Bu	63
Me	Me	Me	iso-Bu	58

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