Tetrahedron Letters No. 40, pp 3907 - 3910, 1973. Pergamon Press. Printed in Great Britain.

MODES OF REACTION OF GRIGNARD REAGENTS WITH CARBAMATES

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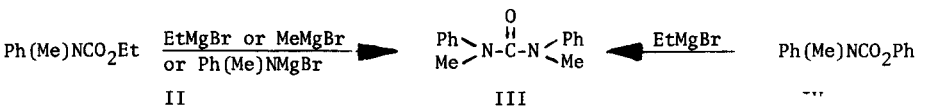
(Received in UK 3 August 1973; accepted for publication 24 August 1973)

Although the reactions of Grignard reagents with amides and esters are well documented[1], very little has been published on their reactions with carbamates $R^1R^2NCOOR^3$ (I) which contain both ester and amide functions. Zerewitinoff[2] reported the determination of active hydrogen of urethan (I, $R^1 = R^2 = H$, $R^3 = Et$) by the use of RMgX. Hoch and Klein[3] reported the reaction of N-cyclohexylideneurethan with aryl- and alkyl-magnesium halides in which the respective N-cyclohexylidene amides were formed, and identified, after hydrolysis, as the corresponding amides. They have also noted that N-benzhydrylidene urethane gave unidentified products which, however, were not the expected amides. Binaghi[4] has isolated halomagnesium salts derived from the reactions of urethan and N-phenylurethan (I, R^1 = Ph, $R^2 = H$, $R^3 = Et$) with ethyl-magnesium bromide and reported their reactions with aldehydes, ketones and acyl halides.

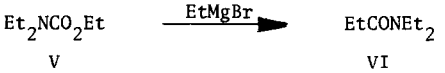
We wish to report in this letter reactions of Grignard reagents with carbamates carrying various substituents on the nitrogen atom, resulting in the formation of a di- or tetra-substituted urea derivative, or of a substituted mono-amide derivative, or of a substituted malonamide derivative.

Ethyl N-methylcarbanilate (II) gave, with both methyl- and ethyl-magnesium bromide in T.H.F. at reflux, 1,3-dimethyl-1,3-diphenylurea (III, 41%), m.p. 122° (lit.[5] 121°) (50% carbamate recovered).

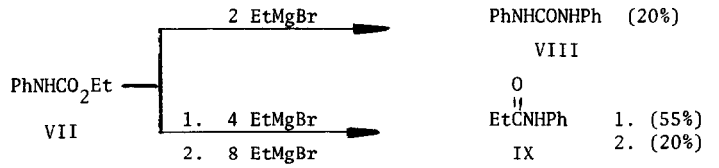


The molar ratios of Grignard reagent to carbamate ranged from 1:1.7 to 2:1 which did not affect the results in this case. The reaction of phenyl N-methylcarbanilate (IV) with EtMgBr also gave III (32% distilled product).

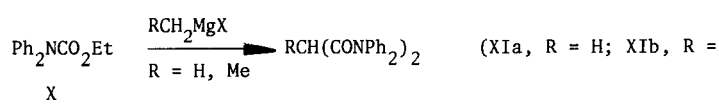
A different result, similar to that reported by Klein and Hoch[3], was observed in the reaction of ethyl N,N-diethylcarbamate (V) with EtMgBr (1:2), in which N,N-diethylpropionamide formed (VI)(28%). This product was identical to a sample prepared seperately[6]. No tetraethylurea could be found among the reaction products. A substantial amount of V was recovered.



Ethyl N-phenylcarbamate (VII) reacted in either of the two above described manners depending on ratio of the Grignard reagent to carbamate. At a ratio of 2:1 the product was 1,3-diphenylurea (VIII, 20%), whereas at ratios of 4:1 and 8:1 the product was propionanilide (IX).



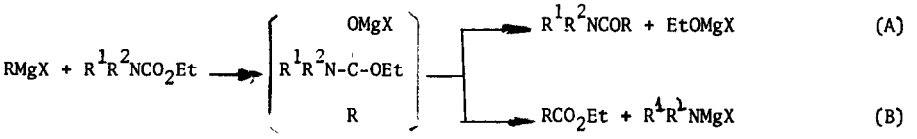
Ethyl N,N-diphenylcarbamate (X) reacted altogether differently. With methylmagnesium bromide, (X) gave N,N,N',N'-tetraphenylmalonamide (12%, most of X recovered)(XIa, m.p. 228°; lit.[7] 220°), δ ($CECl_3$): 3.11]s, $\underline{CH}_2(CONPh_2)_2$] 7.11 [broad m, $CH_2(CO\underline{NPh}_2)_2$]. Found: C, 79.50; H, 5.48; N, 6.89; M^+, 406±1. Requires: C, 79.78; H, 5.46; N, 6.89%; M^+, 406



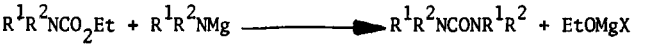
With ethylmagnesium bromide, λ gave N,N,N',N'-tetraphenylmethylmalonamide (XIb), (13%, most of X recovered) m.p. 205°, δ ($CDCl_3$): 1.3 (d, $\underline{CH}_3$-CH); 3.8 (q, CH_3-$\underline{CH}$); 7.2 [broad m, $CH_3CH(CO\underline{NPh}_2)_2$]. Found: C, 79.88; H, 5.64; N, 6.55; M^+, 421±1. Requires: C, 79.98; H, 5.75; N, 6.66%; M^+, 420.

The IR, NMR and mass spectra of XIa were identical to those of N,N,N',N'-tetraphenylmalonamide[7] prepared from malonyl chloride and diphenylamine.

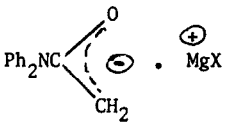
As nucleophilic agents, Grignard reagents can attack certain amido and imido derivatives in more than one fashion, on either side of the carbonyl group, e.g. in case of aziridinones[8,9], aziridinecarbamates[10] and some isocyanates[11]. With carbamates, attack on the carbonyl may result in the expulsion of an alkoxy anion (route A) or an amino anion (route B), both routes possibly involving the tetrahedral intermediate shown in square brackets:



Urea may be formed from unchanged carbamate and the aminomagnesium reagent obtained in route B:



This is the amino-Grignard analogue of route A. In a separate experiment we could indeed get 1,3-dimethyl-1,3-diphenylurea (III) from the reaction of II with N-methylanilinomagnesium bromide - prepared according to Hauser and Walker[12].

The formation of malonate derivatives (XIa and XIb) involves further complications. Reaction of X with, for instance, CH_3MgBr may result in the formation of an enolate magnesium salt  . Nucleophilic attack of this enolate at the carbonyl group of more Ph_2NCO_2Et will lead to formation of $Ph_2NCCH_2CNPh_2$ + EtOMgX, again in analogy to route A. Formation of intermediate enolates has been suggested with strong evidence to rationalize reactions of RMgX with benzalacetophenones[13].

For $RNHCO_2Et$, intermediacy of isocyanates cannot be ruled out and the fact that N-benzoylbenzamide (PhCONHCOPh) is formed in substantial amounts[11] from benzoylisocyanate and butyl- or cyclohexyl-magnesium bromide shows the ease of such reactions.

Obviously the nature of the groups R^1 and R^2 in the carbamates controls the reaction routes more profoundly than could be prima facie expected from accepted electronic effects influencing the leaving ability and/or reactivity of the different groups involved. Work is being continued to clarify the mechanisms.

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