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ORGANOMAGNESIUM COMPOUNDS OF THE ISOXAZOLE SERIES

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Although in recent years organomagnesium compounds of certain nitrogen-containing heterocycles (pyridine, thiazole, pyrazole) have been obtained (^{1,2}), in the isoxazole series they have hitherto remained unknown, which was partly, undoubtedly, connected with the lability of the isoxazole ring toward vigorous nucleophilic reagents.

At the present time we have succeeded for the first time in obtaining organomagnesium compounds of 3,5-dimethylisoxazole and in showing that they behave normally in the Grignard reaction. As in other cases involving nitrogen heterocycles (^{1,2}), halomagnesium isoxazoles are obtained on interaction of 3,5-dimethyl-4-bromo- and 3,5-dimethyl-4-iodoisoxazole with magnesium only under entrainment-reaction conditions in the presence of ethyl bromide, in the solvents customary for organomagnesium synthesis. This reaction was studied by us under various conditions, the yield of the organomagnesium compound formed being determined from the yield of 3,5-dimethylisoxazole-4-carboxylic acid (I), obtained on carbonation and found to be completely identical with a known sample (^{3}):

$$\text{3,5-dimethyl-4-haloisoxazole} \xrightarrow[C_2H_5Br]{Mg} \text{3,5-dimethyl-4-halomagnesium isoxazole} \xrightarrow{CO_2} \text{3,5-dimethylisoxaz}$$

The results of the experiments performed are summarized in Table 1. The data presented indicate that the use of the iodide gives considerably better results than the use of the bromide, and the yield of halomagnesium isoxazole depends on the amount of ethyl bromide taken as the entraining agent. It is most convenient to use a twofold excess of the latter, since, as the experiments showed, a further increase in the amount of ethyl bromide does not lead to an increase in the yield, but makes the isolation of the isoxazolecarboxylic acid more laborious. Replacement of diethyl ether by tetrahydrofuran increases the yield only very slightly, although in this case only 1 equivalent of ethyl bromide may be used, whereas in dibutyl ether the organomagnesium compound cannot be obtained because of resinification of the reaction mixture. Preparatively, the most convenient procedure is the interaction of the haloisoxazole with magnesium in ether in the presence of two equivalents of ethyl bromide, and this was what we used subsequently in the work.

The halomagnesium isoxazoles obtained can be used in typical Grignard syntheses. Thus, we carried out reactions with benzaldehyde and benzophenone, which led to the corresponding arylisoxazolylcarbinols (II and III):

$$\text{3,5-dimethyl-4-iodomagnesium isoxazole} + C_6H_5COR \longrightarrow \text{arylisoxazolylcarbinol} \qquad \begin{array}{l} R = H \text{ (II)} \\ R = C_6H_5 \text{ (III)} \end{array}$$

These results show that organomagnesium compounds of the isoxazole series possess a fairly high reactivity, exceeding, in particular, that of the corresponding pyridine derivatives (1). As indicated above, 3,5-dimethyl-4-iodoisoxazole gives an organomagnesium derivative in higher yield than the corresponding bromide; however, until now there has been no convenient method for the synthesis of iodoisoxazoles. Therefore, in connection with our study of haloorganomagnesium isoxazoles, we specially developed the preparation of 3,5-dimethyl-4-iodoisoxazole (IV) by direct iodination of 3,5-dimethylisoxazole—by the action of iodine in the presence of nitric acid—with a yield of 85%:

$$3,5\text{-dimethylisoxazole} \xrightarrow[\text{HNO}_3\ (d\ 1.5)]{\text{J}_2} 3,5\text{-dimethyl-4-iodoisoxazole}\ (IV)$$

Table 1

Preparation of 3,5-dimethylisoxazole-4-carboxylic acid from 3,5-dimethyl-4-haloisoxazoles

Experiment No.	X	Amount of ethyl bromide, C_2H_5Br, per 1 equiv. of halo-isoxazole	Solvent	Acid yield, %
1	Br	1	Diethyl ether	15
2	Br	2	»	32
3	Br	2	Dibutyl ether	–

Experiment No.	X	Amount of ethyl bromide, C_2H_5Br, per 1 equiv. of halo-isoxazole	Solvent	Acid yield, %
4	J	1	Diethyl ether	36
5	J	2	»	53
6	J	1	Tetrahydrofuran	56
7	J	2	»	57

This substitution reaction, new for isoxazoles, will in all probability serve as a general method for the synthesis of previously unknown iodoisoxazoles, which will be discussed in subsequent communications.

Since the high sensitivity of the isoxazole nucleus to nucleophilic reagents and the effect of substituents on the degree of this sensitivity are well known, it could be expected that the ability of isoxazoles to form organomagnesium compounds would be limited in a definite way. This found partial confirmation in an attempt to obtain the organomagnesium derivative of diphenylisoxazole. 3,5-Diphenyl-4-chloroisoxazole (VI) was synthesized by us according to the scheme:

$$C_6H_5COCH_2COC_6H_5 \xrightarrow{SO_2Cl_2} C_6H_5COCHClCOC_6H_5\ (V) \xrightarrow{NH_2OH} 3,5\text{-diphenyl-4-chloroisoxazole}\ (VI)$$

Dibenzoylmethane was chlorinated with sulfuryl chloride, and the chloride obtained in 86% yield was cyclized by the action of hydroxylamine to chloroisoxazole VI.

It should be noted that the analogous cyclization of dibenzoyliodomethane could not be carried out, since hydroxylamine reduced the iodide to the starting dibenzoylmethane (cf. (4)).

When chloride VI was treated with magnesium under the optimal conditions of organomagnesium synthesis found by us, dibenzoylchloromethane was isolated as the sole reaction product, identical with a previously obtained sample. The mechanism of cleavage of the isoxazole ring under these conditions remains unknown for the time being; at present we are continuing our investigation of the Grignard reaction and related reactions in the isoxazole series.

Experimental Part

3,5-Dimethyl-4-iodoisoxazole (IV). To a solution of 37.3 g (0.147 mole) of iodine in 31.3 g (0.322 mole) of 3,5-dimethylisoxazole, with vigorous stirring and heating on a water bath, is added dropwise

13.6 ml (20.4 g, 0.324 mole) of nitric acid (*d* 1.5). After the addition, the reaction mixture is heated for 30 min on a boiling water bath (decolorization is observed), cooled, and the precipitated crystals are filtered off, washed on the filter with 10% NaOH solution (to remove nitroisoxazole impurity), with water, and dried. Yield 55.4 g (85%), m.p. 51.5–53°, literature data (^{5}): m.p. 52.5–54°.

Found, %: C 27.00; 26.77; H 2.95; 3.01
C_5H_6JNO. Calculated, %: C 26.94; H 2.71.

3,5-Dimethylisoxazole-4-carboxylic acid (I). To 2.7 g (0.112 g-atom) of magnesium, covered with a layer of 20 ml of anhydrous ether, with vigorous stirring, 1.5 g of ethyl bromide (from a total amount of 8.15 g—0.075 mole) is added dropwise, and then a solution of 8.3 g (0.037 mole) of IV and the remaining amount of ethyl bromide in 25 ml of ether is added at such a rate that the ether boils uniformly. The mixture is then boiled for another hour, cooled, solid carbon dioxide is added, and it is acidified with hydrochloric acid (1 : 1). The ether layer and ether extracts from the aqueous layer are shaken for several minutes in a separatory funnel with 10% NaOH solution. The alkaline layer is separated and neutralized with hydrochloric acid (1 : 1); the precipitated acid is filtered off and dried. Yield 2.77 g (53%), m.p. 141.5–142°; a mixed sample with an authentic specimen (^{3}) gives no depression of the melting point. The results of experiments under other conditions are given in Table 1.

3,5-Dimethyl-4-isoxazolylphenylcarbinol (II). To a solution of the organomagnesium compound, prepared analogously to that described above from 11.15 g (0.05 mole) of IV, 10.9 g (0.1 mole) of ethyl bromide, and 3.6 g (0.15 g-atom) of magnesium in 70 ml of ether, with cooling (0°) and stirring, a solution of 9.25 g (0.087 mole) of benzaldehyde in 20 ml of ether is added dropwise. The mixture is then boiled for 2 hours, cooled, and decomposed with hydrochloric acid (1 : 1). The ether layer is separated and dried over magnesium sulfate; after removal of the solvent and distillation of the residue in vacuum, 2.6 g of 3,5-dimethylisoxazole and 1.0 g of II are obtained, boiling at 145–152°/3 mm. Redistillation gives 0.8 g of II (17% based on the isoxazole that entered into the reaction), b.p. 150–152°/3 mm; m.p. 52.5–53.5° (from an ether + *n*-pentane mixture).

Found, %: C 71.41; 71.27; H 6.46; 6.83; N 7.13; 7.17
$C_{12}H_{13}NO_2$. Calculated, %: C 70.92; H 6.45; N 6.89.

3,5-Dimethyl-4-isoxazolyldiphenylcarbinol (III). To a solution of the organomagnesium compound, prepared analogously from 11.15 g of IV, 10.9 g of ethyl bromide, and 3.6 g of magnesium in 50 ml of ether, with cooling (0°) and stirring, a solution of 27.3 g (0.15 mole) of benzophenone in 40 ml of ether is added dropwise. After boiling for two hours, the mixture is decomposed with hydrochloric acid (1 : 1); the precipitated solid (3.4 g) is filtered off and the ether layer is separated and dried over magnesium sulfate. After removal of the solvent, the residue is subjected to fractional crystallization from aqueous methanol and an additional 2.6 g of III is obtained. Total yield 6 g (43%), m.p. 140–141° (from aqueous methanol).

Found, %: C 77.17; 77.31; H 6.24; 6.25
$C_{18}H_{17}NO_2$. Calculated, %: C 77.41; H 6.14.

Dibenzoylchloromethane (V). To a solution of 14.4 g (0.064 mole) of dibenzoylmethane in 100 ml of glacial acetic acid, with stirring, 8.67 g (0.064 mole) of sulfuryl chloride is added dropwise; then the reaction mixture is heated for 2.5 hours at 50°, cooled, and strongly diluted with water. The precipitated solid is filtered off and dried; 14.33 g (86%) of V with m.p. 87–88° is obtained; literature data (6): m.p. 87–88°.

3,5-Diphenyl-4-chloroisoxazole (VI). A solution of 9.16 g (0.035 mole) of V and 2.75 g (0.04 mole) of hydroxylamine hydrochloride in 50 ml of methanol is boiled for 5 hours, cooled, the precipitate that has separated is filtered off, and the filtrate is evaporated. Yield: 8.2 g of VI (91%), m.p. 84° (from methanol).

Found, %: C 70.07; 69.92; H 4.23; 4.23; N 5.50; 5.33
$C_{15}H_{10}ClNO$. Calculated, %: C 70.46; H 3.94; N 5.48.

Reaction of VI with magnesium in the presence of ethyl bromide. To 0.72 g (0.03 g-atom) of magnesium under a layer of 15 ml of ether, a solution of 2.55 g (0.01 mole) of VI and 2.2 g (0.02 mole) of ethyl bromide in 30 ml of ether is added dropwise, and then the mixture is boiled for 5 hours. After the treatment described for the preparation of 3,5-dimethylisoxazole-4-carboxylic acid, 1 g of dibenzoylchloromethane with m.p. 86–87° was isolated; a mixed sample with an authentic specimen gives no depression of the melting point.

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Note: Figure translations are in progress. See original paper for figures.