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Reaction of Amide Homologs. XXV.[1] Reaction of Succinimide with Grignard Reagents

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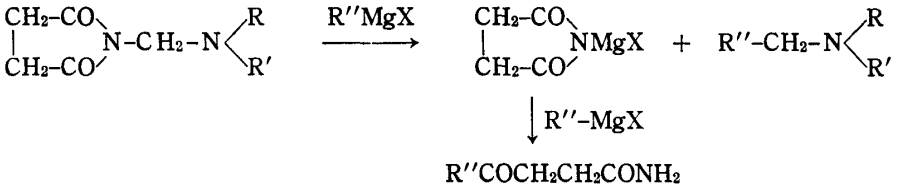
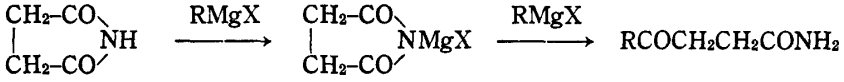
An investigation of Grignard reaction of succinimide revealed that, when more than one molar equivalent amount of Grignard reagent was used, a reaction proceeds to give γ-ketoamide. Using a variety of aliphatic and aromatic Grignard reagents this reaction has been generalized and provided a useful method for preparation of γ-ketoamides.

In the previous paper[1] of this series it has been reported that N-(N′,N′-dialkylaminomethyl) succinimide reacts with two molar equivalent of Grignard reagents to give tertiary amines and γ-ketoamides. It was presumed that the reaction proceeds through an intermediate, a salt-like succinimidomagnesium bromide, formed by nucleophilic substitution reaction with Grignard reagent and formation of γ-ketoamide is effected by the reaction of this intermediate with Grignard reagent, as shown in the following.



In view of this work it was expected that the formation of γ-ketoamide may be also effected by the reaction of succinimide with two molar equivalent of Grignard reagent, where the succinimidomagnesium bromide would be initially formed as an intermediate by attack of the first half of the Grignard reagent. In literature there has been no report on the Grignard reaction of succinimide other than the reaction[3] of N-methylsuccinimide which is described to give 5-alkyl-5-hydroxy-1-methyl-2-pyrrolidinone or 2-alkyl-1-methyl-2-pyrrolin-5-one. Nevertheless, with the above expectation we commenced an investigation on the Grignard reaction of succinimide to open a method for preparation of γ-ketoamides.



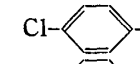
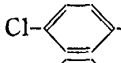
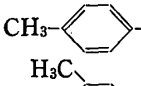
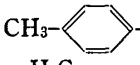
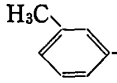
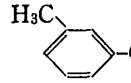
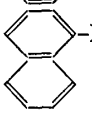
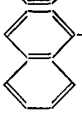
Reactions of succinimide were conducted with a variety of aliphatic and aromatic Grignard reagents under the following uniform conditions: an ethereal Grignard reagent prepared from 2.4-fold molar equivalent amount of a starting bromide was added dropwise to a stirring suspension of succinimide in ether under refluxing and the refluxing was continued for 30 min. Results of experiments are summarized in Table I. As can be seen, the corresponding γ-ketoamides were successfully obtained more than 40% yield. In comparison with the reactions of N-(piperidinomethyl) succinimide with the Grignard reagents previously reported,[1] the

1) Part XXIV: M. Sekiya and Y. Terao, *Chem. Pharm. Bull.* (Tokyo), **18**, 947 (1970).
2) Location: *2-2-1, Oshika, Shizuoka.*
3) R. Lukes, *Chem. Listy*, **22**, 1 (1928) [*C.A.*, **22**, 1773 (1928)]; R. Lukes and V. Prelog, *ibid.*, **22**, 244 (1928) [*C.A.*, **23**, 1408 (1929)]; E. Walton, *J. Chem. Soc.*, **1940**, 438.

products, 2-benzoylpropionamide, 2-(2-phenylpropionyl) propionamide and 2-pentoylpropionamide were obtained in better yield by this reaction, as described in Table I.

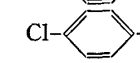
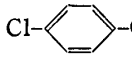
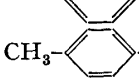
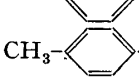
To the use of this reaction for preparative purpose a disadvantage is the consumption of the first half of the Grignard reagent in the course of the formation of the succinimidomagnesium bromide. To diminish this disadvantage we made an improvement in the reaction by substitution of the more inexpensive Grignard reagent, such as ethylmagnesium bromide, in place of the first half of the Grignard reagent. The procedure is that, instead of the addition of 2.4-fold molar equivalent amount of the Grignard reagent in the foregoing procedure, 1.2 molar equivalent amount of ethylmagnesium bromide was first added so as to form suc-

Table I. Reaction[a] of Succinimide with Grignard Reagents

Grignard reagent	Product	Yield[b] (%)
		65(61)[c]
		54(35)[c]
$CH_3(CH_2)_2CH_2MgBr$	$CH_3(CH_2)_2CH_2COCH_2CH_2CONH_2$	50(33)[c]
$(CH_3)_2CHCH_2CH_2MgBr$	$(CH_3)_2CHCH_2CH_2COCH_2CH_2CONH_2$	48
CH_3CH_2MgBr	$CH_3CH_2COCH_2CH_2CONH_2$	35
		41
		59
		69
		64
		47
		60

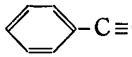
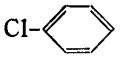
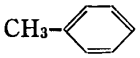
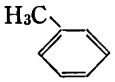
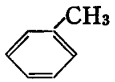
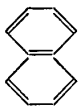
a) General procedure is given in Experimental.
b) Yield is based on the product isolated.
c) Yield in the reaction of N-(piperidinomethyl)succinimide, which is quoted from the previously reported paper.[1]

Table II. Reaction[a] of Succinimidomagnesium Bromide with Grignard Reagent

Grignard reagent	Product	Yield[b] (%)
		63
		40
		55
		62
		66

a) Succinimidomagnesium bromide in ether, which was freshly prepared by the reaction of succinimide with 1.2 molar equiv. of ethylmagnesium bromide, was subjected to the reaction with Grignard reagent. General procedure is given in Experimental.
b) Yield is based on the product isolated.

TABLE III. Physical and Spectral Data of $RCOCH_2CH_2CONH_2$

Compound (R)	Appearance (recryst. solv.)	mp (°C)	UV λ_{max}^{MeOH} mμ (ε)	IR ν cm^{-1} Band assign.	IR ν cm^{-1} KBr disk	IR ν cm^{-1} $CHCl_3$ solun.	Formula	Analysis (%) Calcd. / Found C	H	N
C_2H_5	plats (EtOH)	95—96		NH_2	3342 3162	3519 3406	$C_6H_{11}O_2N$	55.79 56.04	8.58 8.52	10.85 10.81
				ketone C=O	1710	1710				
				amide C=O	1658	1679				
$(CH_3)_2CHCH_2CH_2$	plats (EtOH)	117—118		NH_2	3342 3162	3518 3407	$C_9H_{17}O_2N$	63.13 63.05	10.00 9.90	8.18 8.38
				ketone C=O	1706	1708				
				amide C=O	1655	1674				
	plats (EtOH)	85—86	272.5 (2.08×10^4) 281.5 (1.28×10^4)	NH_2	3384 3180	3514 3400	$C_{12}H_{11}O_2N$	71.62 71.46	5.51 5.76	6.96 6.35
				-C≡C-	2202	2202				
				ketone C=O	1664	1683				
				amide C=O	1636	1670				
	plats (EtOH)	160—161	250.5 (2.50×10^4) 287.0 (0.85×10^3)	NH_2	3362 3160	3516 3403	$C_{10}H_{10}O_2NCl$	56.74 56.85	4.76 4.96	6.61 6.28
				ketone C=O amide C=O	1670 1646	1685				
	plats (EtOH)	171—173	252.3 (1.51×10^4) 288.0 (0.86×10^3)	NH_2	3376 3172	3514 3404	$C_{11}H_{13}O_2N$	69.09 69.02	6.85 6.92	7.33 7.11
				ketone C=O amide C=O	1679 1649	1682				
	needles (EtOH)	124—125	245.5 (1.38×10^4) 287.0 (1.32×10^3)	NH_2	3372 3159	3518 3404	$C_{11}H_{13}O_2N$	69.09 69.04	6.85 6.72	7.33 7.25
				ketone C=O amide C=O	1673 1648	1678				
	prisms	105—106	241.8 (1.32×10^4) 283.0 (1.18×10^3)	NH_2	3367 3128	3518 3381	$C_{11}H_{13}O_2N$	69.09 68.95	6.85 6.82	7.33 7.21
				ketone C=O amide C=O	1686 1663	1681				
	prisms (EtOH)	157—159	299.0 (1.83×10^4)	NH_2	3352 3145	3513 3398	$C_{14}H_{13}O_2N$	73.99 73.98	5.77 5.91	6.16 5.62
				ketone C=O amide C=O	1681 1658	1678				

cinimidomagnesium bromide and then addition of equimolar amount of the requisite Grignard reagent was followed. This procedure was examined in several examples and results are summarized in Table II. As can be seen from this Table, this procedure attained the almost same yields of γ-ketoamides as those in the foregoing procedure.

Thus, the present work has developed a new general method for preparation of γ-ketoamides better than the previously reported method[1] through the reaction of N-(N',N'-dialkylaminomethyl)succinimide.

On referring to the previous paper,[1] identities of the γ-ketoamides obtained in the present work were made by their ultraviolet (UV) and infrared (IR) spectral data, which showed well agreement with the assigned γ-ketoamide structures (see Table III). Among the γ-ketoamides obtained, those listed in the Table III have not been described previously.

Experimental

Reactions of Succinimide with Grignard Reagent——a) General Procedure: Grignard reagents which are listed in Table I were prepared by usual means from 0.155 gram atom of magnesium, 0.144 mole each of the alkyl halides and 200 ml of dry ether, with an exception of phenylethynylmagnesium bromide, which was prepared by admixture of ethereal solution of 0.144 mole of phenylacetylene to the ethylmagnesium bromide solution prepared by the above way. To a suspension of 0.06 mole of pulverized succinimide in 100 ml of dry ether the Grignard reagent was added dropwise with vigorous stirring under spontanious refluxing. During the addition of the second half of the reagent, heating was necessary for refluxing. Stirring and refluxing were continued for further 30 min and the reaction mixture was hydrolyzed by addition of aqueous NH_4Cl in an ice bath. The product, γ-ketoamide, was deposited in the hydrolyzed solution mostly in the case of using aromatic halide and collected by filteration. The remaining product was isolated by concentration of the ethereal layer and by extraction of the aqueous layer with $CHCl_3$. 2-Propionylpropionamide, obtained in the run with ethylmagnesium bromide, was isolated by extraction with $CHCl_3$ using a continuous extraction apparatus because of its easy solubility in water. Yields of the products are listed in Table I. Identities of the γ-ketoamides obtained were made by elemental analysis and by measurement their UV and IR spectra on refering to the previous paper.[1] The three products, 2-benzoylpropionamide, 2-(2-phenylpropionyl)propionamide and 2-pentoylpropionamide, which had been described in the previous paper,[1] showed exact correspondence of their physical data with those of the authentic specimens. Excepting these three compounds the other eight γ-ketoamides have not been described previously. Their physical and analytical data are recorded in Table III.

b) Modified Procedure: To a suspension of 0.06 mole of pulverized succinimide in 100 ml of dry ether ethylmagnesium bromide (prepared from 0.08 gram atom of magnesium, 0.072 mole of ethyl bromide and 100 ml of dry ether) was added dropwise under vigorous stirring. The mixture refluxed with stirring for 30 min so as to form succinimidomagnesium bromide. And then to the mixture the requisite Grignard reagent (prepared from 0.08 gram atom of magnesium, 0.072 mole of alkyl halide and 100 ml of dry ether) was added dropwise with vigorous stirring under refluxing. The reaction mixture was stirred and refluxed for further 30 min and then hydrolyzed by means of addition of aqueous NH_4Cl and the product was isolated by the same manner as described in the above procedure. This procedure was examined using the Grignard reagents listed in Table II and resulted in as summarized in the same Table. Identities of the products, γ-ketoamides were made by comparison of their IR spectra with those of the authentic specimens obtained procedure a).

Acknowledgement We are grateful to the members of Analytical Center of this college for their elemental analysis and spectral measurements.