Grignard Reagents. XXIV. The Behavior of 3-Keto Derivatives of 1,2,4-Triazines toward Organomagnesium Halides, Lithium Aluminum Hydride, and *p*-Thiocresol

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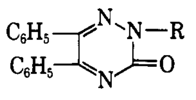
Received March 9, 1962

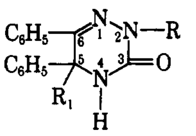
3-Hydroxy-5,6-diphenyl-1,2,4-triazine (Ia) and 2-substituted derivatives (Ib–Id) react with alkyl- and aralkylmagnesium halides to form 3-hydroxy-5-alkyl-5,6-diphenyl-4,5-dihydro-1,2,4-triazine (IIa–IIc), and 2-substituted 3-keto-5-alkyl(or aralkyl)-5,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazines (IId–IIj), respectively. Similarly, treatment of 7-methyl-3-keto-2-*p*-tolyl-2,3-dihydro-1,2,4-benzotriazine (III) and 2-aryl-3-keto-2,3-dihydronaphtho[2.1]-1,2,4-triazines (V) with Grignard reagents led to the formation of IV and VI, respectively. The reactivity of the C=N in position 4,5 in Ia–Ic has been further illustrated by its ready reduction with lithium aluminum hydride and/or *p*-thiocresol to give the corresponding tetrahydro derivatives (IIk–IIm).

Less attention has been directed to the reactions of substituted 3-hydroxy-5,6-diphenyl-1,2,4-triazines (I) than to their preparation. In general reduction and alkylation are the reactions that have been most extensively investigated.[1] The discussion that follows will form a part of investigation that started in this department to study the chemical properties of this class of compounds.

In continuation of the work of one of the authors[2] on the action of organomagnesium compounds on heterocyclic compounds, the behavior of I toward the same reagents has been undertaken. Thus, when Ia was treated with alkylmagnesium halides, namely, methyl-, ethyl-, and *n*-butylmagnesium iodide, followed by hydrolysis, 3-hydroxy-5-alkyl-5,6-diphenyl-4,5-dihydro-1,2,4-triazines (IIa–IIc) were obtained.



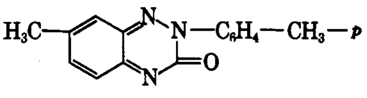
Ia, R = H (or tautomer)
b, R = CH_3
c, R = C_2H_5
d, R = C_6H_5



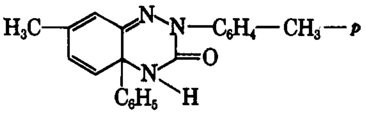
IIa, R = H; R_1 = CH_3
b, R = H; R_1 = C_2H_5
c, R = H; R_1 = n-C_4H_9
d, R = R_1 = CH_3
e, R = CH_3; R_1 = C_2H_5
f, R = C_6H_5; R_1 = C_2H_5
g, R = C_2H_5; R_1 = CH_3
h, R = R_1 = C_2H_5
i, R = C_6H_5; R_1 = CH_3
j, R = CH_3; R_1 = $CH_2C_6H_5$
k, R = R_1 = H
l, R = CH_3; R_1 = H
m, R = C_2H_5; R_1 = H

Similarly, treatment of 2-methyl- (Ib), 2-ethyl- (Ic), and 2,5,6-triphenyl-3-keto-2,3-dihydro-1,2,4-triazine (Id) with methyl- and/or ethylmagnesium iodide led to the formation of the corresponding 2-substituted 3-keto-5-alkyl-5,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazines (IId–IIi). 2-Methyl-3-keto-5-benzyl-5,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine (IIj) has been obtained by the action of benzylmagnesium chloride on Ib.

Whereas treatment of 3-substituted 3,4-dihydro-4-keto-1,2,3-benzotriazines with Grignard reagents leads to the opening of the heterocyclic ring with the formation of *o*-phenyldiazoaminotriarylcarbinols,[2] we have found that the heterocyclic ring in 7-methyl-3-keto-2-*p*-tolyl-2,3-dihydro-1,2,4-benzotriazine(III) is not opened by the action of the same reagents and addition to the C=N in position 4,5 takes place[3] with the formation of IV. The stability of the heterocyclic ring simulates the stability of 3,4-dihydro-4-keto-1,2,3-benzotriazine when placed in the Grignard machine.[2]



III



IV

3-Keto-2-aryl-2,3-dihydronaphtho[2.1]-1,2,4-triazines (V) behave similarly when allowed to react with phenylmagnesium bromide yielding VIa, VIc–VIe. Compounds VIb and VIf are readily obtained by the action of ethylmagnesium iodide on Va and Vf, respectively.

The assigned structure for the Grignard products is inferred from the facts that (a) they give the correct analytical values, (b) are insoluble in dilute alkali (*cf.* the ready solubility of Ia in dilute alkali and the insolubility of the corresponding reduced product[1] IIk, (c) the infrared spectra of IIa–IIb are similar with that of the known IIk, and (d) a dibenzoyl derivative is formed when IIb is treated with benzoyl chloride (see Table I).

The nuclear magnetic resonance measurements are in favor of the proposed structure IIa. The spectra are measured at 60 Mc. in about 10% dimethyl sulfoxide solution. The p.p.m. values are referred to tetramethylsilane as zero as an internal standard. For compound IIk the signal for the hydrogen proton at N-2 appears at 10.26 p.p.m.; the signal for the proton at N-4 appears at 8.2 p.p.m., which through coupling with the hydrogen at C-5 (5.76 p.p.m.) suffers a splitting of 3.5 p.p.m. From 7–7.8 p.p.m., the protons of both benzene rings lie within their corresponding intensities. The intensity ratio are shown in the spectra. The hydrogens at N-2 and N-4 are exchangeable with that in

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[1] J. G. Erickson, P. F. Wiley, and V. P. Wystrach, "The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines," Interscience Publishers, Inc. New York, N. Y., 1957.

[2] A. Mustafa, W. Asker, A. M. Fleifel, S. Khattab, and S. Sherif, *J. Org. Chem.*, **25**, 1501 (1960).

[3] *Cf.* the ready addition of hydrogen to the 4,5-position of Ia to form IIk: H. Biltz and C. Stellbaum, *Ann.*, **339**, 281 (1905).

TABLE I

GRIGNARD PRODUCTS FROM 3-KETO-1,2,4-TRIAZINES

Grignard products[a]	Solvent for crystallization[b]	M.p.,[c] °C.	Yield, %	Formula	Analysis, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
IIa	A	268	71	$C_{16}H_{15}N_3O$	72.45	72.93	5.66	6.00	15.84	15.95
IIb	B	278–279	75	$C_{17}H_{17}N_3O$	73.11	73.07	6.09	6.14	15.05	14.99
IIc	A	267	61	$C_{19}H_{21}N_3O$	74.26	73.87	6.84	6.97	13.68	13.62
IId	A	178	67	$C_{17}H_{17}N_3O$	73.11	72.85	6.09	6.04	15.05	15.61
IIe	A	172	69	$C_{18}H_{19}N_3O$	73.72	73.56	6.48	6.23	14.33	14.12
IIf	A	160	59	$C_{23}H_{21}N_3O$	77.75	77.69	5.91	6.20	11.83	11.47
IIg	A	175	81	$C_{18}H_{19}N_3O$	73.72	73.52	6.48	6.66	14.33	14.11
IIh	A	150	79	$C_{19}H_{21}N_3O$	74.26	74.60	6.84	6.89	13.68	13.20
IIi	A	152	62	$C_{22}H_{19}N_3O$	77.42	76.94	5.57	5.81	12.31	12.06
IIj	A	180	72	$C_{23}H_{21}N_3O$	77.74	77.53	5.91	5.88	11.83	12.50
IV	C	234	48	$C_{21}H_{19}N_3O$	76.59	77.30	5.77	5.85	12.76	12.60
VIa	C	245–247	75	$C_{23}H_{17}N_3O$	78.63	78.57	4.84	5.00	11.96	11.96
VIc	C	286	39	$C_{24}H_{19}N_3O$	78.90	79.07	5.20	5.44	11.50	10.83
VId	C	159	29	$C_{23}H_{16}N_3OBr$	64.18	64.71	3.72	3.74	9.76	9.61
VIe	C	291–292	25	$C_{23}H_{16}N_3OCl$	71.59	72.50	4.15	4.57	10.89	10.24
VIf	C	215	47	$C_{20}H_{19}N_3O_2$					12.31	12.37

[a] The Grignard products were insoluble in aqueous sodium hydroxide solution. [b] A is alcohol, B is acetic acid, C is xylene. [c] All melting points are uncorrected.

TABLE II

3-KETO-2-ARYL-2,3-DIHYDRONAPHTHO[2.1]-1,2,4-TRIAZINES (Vb–Vf)

Triazine	Solvent for crystallization[a]	M.p.,[b] °C.	Yield, %	Formula	Analysis, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Vb	A	246	60	$C_{18}H_{13}N_3O$	75.24	74.93	4.56	4.65		
Vc	A	292	55	$C_{17}H_{10}N_3OBr$	57.97	57.45	2.86	3.12	11.93	12.43
Vd	A	198	43	$C_{17}H_{10}N_3OCl$	66.34	66.12	3.27	2.98	13.65	12.99
Ve	B	225	62	$C_{18}H_{13}N_3O$	75.24	74.95	4.56	4.22	14.62	14.41
Vf	A	242	48	$C_{18}H_{13}N_3O_2$	71.27	70.98	4.32	4.11	13.85	13.54

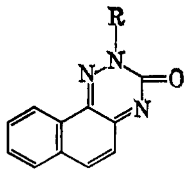
[a] A is xylene, B is alcohol. [b] All melting points are uncorrected.

heavy water, whereby the expected coupling at C-5 disappears.

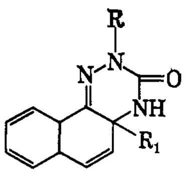
For compound IIa the signal for the hydrogen at N-2 appears at the same place as with compound IIk. The hydrogen at N-4 appears at 7.8 p.p.m.; both protons are exchangeable with deuterium. The aromatic hydrogens appear from 7–7.6 p.p.m. In order to detect the methyl signals, a sample was measured in pyridine, whereby the singlet at 1.00 p.p.m. appears in the right integral ratio.

The spectra of the known compound IIk and the Grignard product IIa show very great similarities; in both cases the slight splitting off of the protons at N-2 (about 2 p.p.m.) may be due to a long-range coupling with the proton at N-4.

That the Grignard product has a structure like VII, involving 1,6-addition of the Grignard reagent to Ia, may be disfavored. In the case of structure VII, a signal for the hydrogen at N-1 should appear (about 4–4.5 p.p.m.) at much higher field strength and the peculiar fine structure for the hydrogen at N-2 might be missing.



Va, R = C_6H_5
b, R = $C_6H_4CH_3$-*p*
c, R = C_6H_4Br-*p*
d, R = C_6H_4Cl-*p*
e, R = $C_6H_4CH_3$-*m*
f, R = $C_6H_4OCH_3$-*p*



VIa, R = R_1 = C_6H_5
b, R = C_6H_5; R_1 = C_2H_5
c, R = $C_6H_4CH_3$-*p*; R_1 = C_6H_5
d, R = C_6H_4Br-*p*; R_1 = C_6H_5
e, R = C_6H_4Cl-*p*; R_1 = C_6H_5
f, R = $C_6H_4OCH_3$-*p*; R_1 = C_2H_5

The reactivity of the C=N in position 4,5 in Ia–Ic has been further illustrated by its ready reduction by the action of lithium aluminum hydride and of *p*-thiocresol to give IIk–IIm, respectively. There is a formal analogy between the action of organomagnesium halides and of lithium aluminum hydride on Ia–Ic. The fact that IIb is recovered when heated with zinc dust and alcohol–acetic acid mixture, under the same conditions which allowed reduction of Ia[3] to IIk, may be considered in favor of the reactivity of the C=N in the 4,5-position.[4] Similarly, compounds IIk–IIm have been obtained by heating Ia–Ic with *p*-thiocresol.

The generally applicable route used for the preparation of the substituted naphtho-3-keto-1,2,4-triazines (Vb–Vf), listed in Table II, involved the reaction of phosgene with the corresponding aminoazo compound.[5]

Experimental

Action of Organomagnesium Halides on 3-Keto Derivatives of 1,2,4-Triazines (*cf.* **Table II**). **General Procedure.**—The following exemplifies the procedure. To a Grignard solution (prepared from 1.0 g. of magnesium, 8.0 g. of ethyl iodide, and 35 ml. of dry ether) was added 2.0 g. of Va and 40 ml. of dry benzene. The reaction mixture was refluxed for 2 hr. and kept overnight at room temperature. It was then decomposed with a cold saturated ammonium chloride solution. The organic layer was sepa-

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[4] The C=O absorption is shifted from 5.95 in Ia to 5.8 μ in IIk; such a shift is characteristic in the conversion of a conjugated C=O to unconjugated C=O. The possibility of the 1,6-addition should not be excluded completely and rigorous structure elucidation is in progress.

[5] M. Busch, *Ber.*, **32**, 2959 (1899).

rated, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue so obtained after evaporation was crystallized from ethanol giving colorless crystals of VIb, m.p. 203–204°; yield, *ca.* 68%.

Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 75.24. H, 5.61; N, 13.86. Found: C, 75.54; H, 5.43; N, 13.90.

Action of Lithium Aluminum Hydride on Ia–Ic. General Procedure.—Lithium aluminum hydride (1.0 g.) was added to 50 ml. of dry ether. The mixture was refluxed for 15 min. and then 1.0 g. of each of the triazines (Ia–Ic) was added followed by 20 ml. of dry benzene. The reaction mixture was refluxed for 2 hr. and kept overnight at room temperature. It was poured into a cold saturated ammonium chloride solution and shaken in a separatory funnel. After separating the organic layer, it was dried over anhydrous sodium sulfate and filtered. After evaporation of the solvent, compounds IIk–IIm were obtained. The products were crystallized from ethanol. Compounds IIk–IIl gave no depression in melting point when each was mixed with an authentic sample.[3]

Anal. Calcd. for $C_{17}H_{17}N_3O$ (compound IIm): C, 73.11; H, 6.09; N, 15.05. Found: C, 72,95; H, 5.96; N, 14.78.

Action of *p*-Thiocresol on Ia–Ic. General Procedure.—The triazine (Ia–Ic, 1.0 g.) was heated (170–180°) with *p*-thiocresol (1.0 g.) for 1.5 hr. The reaction mixture was then cooled, washed several times with hot petroleum ether (b.p. 40–60°), and filtered. The products were crystallized from ethanol and proved to be IIk–IIm (melting point and mixture melting point with authentic samples[3]).

Action of Benzoyl Chloride on IIb.—Two grams of chloroform and 1.8 g. of benzoyl chloride were added to a solution of 1.25 g. of IIb in 2.0 g. of dry pyridine. The reaction mixture was heated (steam bath) for 1 hr. and kept overnight at room temperature. It was then poured into cold water. The oil obtained was extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate, filtered, and evaporated. The colorless solid obtained after evaporation was washed with ethanol and recrystallized from the same solvent into colorless crystals of 3-oxo-5,6-diphenyl-2,4-dibenzoyl-2,3,4,5-tetrahydro-1,2,4-triazine, m.p. 182°; yield, *ca.* 81%.

Anal. Calcd. for $C_{31}H_{25}N_3O_3$: C, 76.38; H, 5.13; N, 8.62. Found: C, 75.67; H, 5.38; N, 8.61.

Action of Zinc and Acetic Acid–Alcohol Mixture on IIb.—To a solution of 1.0 g. of IIb in a mixture of 8 ml. of ethanol and 8 ml. of glacial acetic acid was added 0.6 g. of zinc powder. The reaction mixture was refluxed for 4 hr., filtered, then poured into cold water. The solid obtained was filtered, recrystallized from acetic acid, and proved to be unchanged IIb (melting point and mixture melting point). The yield was almost quantitative.

Acknowledgment.—The authors are indebted to Dr. J. Sonnenbichler of Max-Plank-Institut fur Biochemie for determining and interpreting the mass spectra.

Preparation and Thermal Rearrangement of Alkenyl 3-Alkenyloxy-2-butenoates. Catalysis of the Aliphatic Claisen Rearrangement by Ammonium Chloride

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Received July 29, 1963

The thermal rearrangements of allyl 3-allyloxy-2-butenoate and crotyl 3-crotyloxy-2-butenoate are shown to be first-order intramolecular reactions. The rate constants are $2.7 \times 10^{10}\ e^{-26,300/RT}$ and $5.3 \times 10^{11}\ e^{-28,000/RT}$ sec.$^{-1}$, respectively. The reactions have moderate rates at temperatures as low as 115°. The ΔS^* values of -11.3 and -5.4 e.u. are consistent with a cyclic transition state. All of the probable products and crossed products of the rearrangements have been prepared. No crossed products were detected by analysis of the products of a mixed rearrangement by gas–liquid partition chromatography and infrared spectroscopy. The rearrangements are accelerated to a small degree by heterogeneous catalysis by ammonium chloride. The operation of homogeneous catalysis by ammonium chloride or its dissociation products was excluded as an explanation of the increased rate by a proton magnetic resonance study of the rearrangements.

As a part of a continuing interest in thermal unimolecular reactions[3,4] we have studied the preparation and rearrangement of allyl 3-allyloxy-2-butenoate (**1**) and crotyl 3-crotyloxy-2-butenoate (**2**). Lauer and Kilburn[5] have reported the thermal rearrangement of ethyl 3-allyloxy-2-butenoate (**3**) to ethyl 2-allyl-3-oxobutanoate (**6**) at 150–200°. These workers also confirmed the report by Claisen[6] that this rearrangement took place at a lower temperature in the presence of ammonium chloride. No kinetic data on the rate of this rearrangement have been reported.

The purpose of this study was to establish the presumed intramolecular mechanism for the thermal rearrangement of allylic 3-alkenyloxy-2-butenoates to 2-alkenyl-3-oxobutanoates. A second objective was to define the role of ammonium chloride as a catalyst in the rearrangement. Due to the possibility of ester enol–ether interchange complicating this latter question, we chose to use the compounds **1** and **2** (where R = R′) in place of mixed ester enol–ethers such as **3**.

The desired compounds (**1** and **2**) for this study were prepared by the conjugate addition of unsaturated alcohols to alkenyl 2-butynoates.[7] This addition should produce the isomer in which the CH_3– and H– have a *trans* relationship across the double bond conjugated with the ester carbonyl.[8] The infrared spectra of **1** and **2** support the assignment of the *trans* configuration, but are not completely conclusive. Lecomte and Naves have reported[9] that ionones and irones having a *trans* $H–C{=}C–CH_3$ structure show absorption at 984–999 cm.$^{-1}$. Compounds **1** and **2** have absorption bands at 995 and 990 cm.$^{-1}$, respectively, as would be expected. However, in the case of **1** the band is largely the result of out-of-plane bending vibrations of the allyl substituents.

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[1] A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture, Albany 10, Calif.

[2] Collaborator employed by the National Canners Association with which this work was conducted cooperatively.

[3] J. W. Ralls and C. A. Elliger, *Chem. Ind.* (London), 20 (1961).

[4] J. W. Ralls, C. A. Elliger, and R. E. Lundin, *Vortex*, **22**, 454 (1961).

[5] W. M. Lauer and E. I. Kilburn, *J. Am. Chem. Soc.*, **59**, 2586 (1937).

[6] L. Claisen, *Ber.*, **45**, 3157 (1912).

[7] L. N. Owen [*J. Chem. Soc.*, 385 (1945)] has described the addition of saturated alcohols to tetrolic acid.

[8] W. J. le Noble, *J. Am. Chem. Soc.*, **83**, 3897 (1961).

[9] J. Lecomte and Y. R. Naves, *J. chim. phys.*, **53**, 462 (1956).