[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

1,2 AND 1,4 ADDITIONS OF CINNAMIC ACID DERIVATIVES WITH SODIO KETONES, GRIGNARD REAGENTS, AND METALLIC AMIDES

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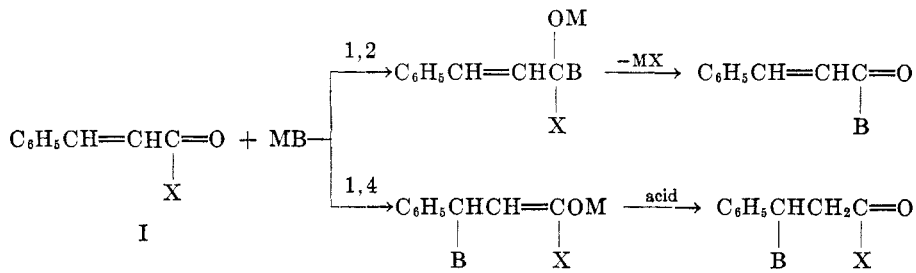
Received October 11, 1948

Cinnamic acid derivatives (I) might exhibit with sodio ketones, Grignard reagents, and metallic amides either 1,2 or 1,4 addition. These two courses of reaction may be illustrated by the following general scheme in which MB represents the basic reagent.



In the present investigation a study has been made of the relative extents of these two courses of reaction with certain of these basic reagents as X in (I) is varied. Although the magnesium of Grignard reagents (and perhaps also the sodium of sodio ketones) may first coordinate with the carbonyl oxygen of (I), the relative extents of formation of the 1,2 and 1,4 addition products are assumed to be dependent on the relative rates of addition of the basic anions at the carbonyl carbon and β-carbon, respectively. Because X is in closer proximity to the carbonyl carbon than to the β-carbon, its electronic and steric effects should influence the rate of the 1,2 addition more than that of the 1,4 addition. Consequently, a variation in X which would decrease the rate of the 1,2 addition should increase the relative extent of the 1,4 addition. The relative rate of the 1,2 addition might be expected to decrease as X is varied in the order, Cl, OC_6H_5, OCH_3 or OC_2H_5, $OC(CH_3)_3$, $N(C_2H_5)_2$, since, with the corresponding acetic or benzoic acid derivatives, this is known to be the decreasing order of the relative ease of alkaline hydrolysis, which may be considered to involve 1,2 addition with sodium hydroxide. Therefore, cinnamic acid derivatives (I) might be expected to exhibit, with a particular basic reagent, relatively less 1,2 addition and relatively more 1,4 addition as X is varied in this order. In general, this expectation has been realized. This can be seen from the results summarized in Table I which are taken from the present investigation and from the literature. Thus with sodio acetophenone, 1,2 addition occurs when X is chlorine and apparently mainly when X is phenoxy whereas 1,4 addition takes place mainly when X is

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methoxy or ethoxy; with phenylmagnesium bromide, 1,2 and 1,4 addition appear to occur to about equal extents when X is phenoxy whereas 1,4 addition is realized largely when X is ethoxy and exclusively when X is *t*-butoxy or diethylamino; with sodium amide, 1,2 addition predominates when X is ethoxy or *t*-butoxy whereas 1,4 addition occurs partly when X is diethylamino; with diethylaminomagnesium bromide, 1,2 addition occurs mainly when X is methoxy whereas 1,4 addition is realized when X is *t*-butoxy. The basis for these generalizations and also certain related reactions are discussed below.

Reactions with sodio ketones. Ryan and Dunlea (1) reported that sodio acetophenone, prepared by means of sodium amide, or sodio acetone, prepared by means of metallic sodium, reacted with ethyl or methyl cinnamate by 1,2 addition to form the corresponding β-diketone. However, in each case the yield was only about 6%. Stobbe (2) reported, that in the presence of sodium ethoxide,

TABLE I

MODE OF ADDITION OF BASIC REAGENTS TO $C_6H_5CH{=}CHCOX$ AS X IS VARIED

REAGENT	Cl	OC_6H_5	(OCH_3) OC_2H_5	$OC(CH_3)_3$	$N(C_2H_5)_2$
$Na(CH_2COC_6H_5)$	1,2	1,2 (1,4?)[a]	1,4 (1,2)[a]		
C_6H_5MgBr	1,2 and 1,4?	1,2 and 1,4	1,4 (1,2)[a]	1,4	1,4
$NaNH_2$			1,2	1,2	1,4 (1,2)[a]
$(C_2H_5)_2NMgBr$			1,2 (1,4?)	1,4	

[a] Realized to a relatively small extent.

acetophenone added to ethyl cinnamate by 1,4 addition to form the Michael condensation product but no yield was given.

In the present investigation, it was found that sodio acetophenone, prepared by means of sodium amide, reacted with methyl or ethyl cinnamate by 1,4 addition to form the Michael condensation product which, on hydrolysis, gave β-phenyl-γ-benzoylbutyric acid (II) in 49% and 66% yield, respectively. Similarly, sodio pinacolone reacted with ethyl cinnamate to give the Michael condensation product in 64% yield. None of the β-diketone which would result from 1,2 addition was found; however, the copper salt method for the isolation of the β-diketone, used by Ryan and Dunlea, was not employed. The main reaction with ethyl cinnamate and sodio acetophenone may be represented as

$$C_6H_5CH{=}CHCO_2C_2H_5 + Na(CH_2COC_6H_5) \rightarrow \left[\begin{array}{c} C_6H_5CHCHCO_2C_2H_5 \\ | \\ CH_2COC_6H_5 \end{array}\right] Na \xrightarrow{+\ \text{acid}}$$

$$\begin{array}{c} C_6H_5CHCH_2CO_2C_2H_5 \\ | \\ CH_2COC_6H_5 \end{array} \xrightarrow[(NaOH)]{HOH} \begin{array}{c} C_6H_5CHCH_2CO_2H \\ | \\ CH_2COC_6H_5 \end{array}$$

II

The yields reported above were obtained using a slight excess (10%) of the sodio ketone. When one molecular equivalent of ethyl cinnamate to one equivalent each of sodio acetophenone and sodium amide was used, the yield of II was lower (37%). The reaction was realized also with a catalytic amount (10 mole %) of sodium amide but the yield was only 19%.

When phenyl cinnamate, in which the carbonyl group is more reactive, sodio acetophenone and sodio acetone reacted by 1,2 addition to give the corresponding β-diketone in yields of 29–30%. Since these reactions were carried out with one molecular equivalent each of the ester and sodio ketone in the presence of an equivalent of sodium amide, the β-diketone was converted to its sodium derivative presumably by the sodium amide (3). The formation of cinnamoylacetophenone (III) may be represented as

$$C_6H_5CH{=}CHCO_2C_6H_5 \xrightarrow[NaNH_2]{NaCH_2COC_6H_5} [C_6H_5CH{=}CHCOCHCOC_6H_5]Na \xrightarrow{acid} C_6H_5CH{=}CHCOCH_2COC_6H_5$$

III

In addition to the β-diketone, there was obtained a considerable quantity of a viscous red oil from which nothing could be crystallized. On refluxing the oil with sodium hydroxide, a small amount (3%) of an acid was obtained which appeared to be β-phenyl-γ-benzoylbutyric acid, presumably resulting from 1,4 addition.

When the reaction was carried out using two equivalents of sodio acetophenone to one of phenyl cinnamate, the yield was considerably lower (15%). In this case, a small amount of white solid was obtained in addition to the yellow cinnamoylacetophenone. The white compound was evidently compound IV, which was formed apparently from both a 1,2 and a 1,4 addition; it has not been established which mode of addition occurred first.

$$C_6H_5CHCH_2COCH_2COC_6H_5$$
$$\quad\quad|$$
$$\quad CH_2COC_6H_5$$

IV

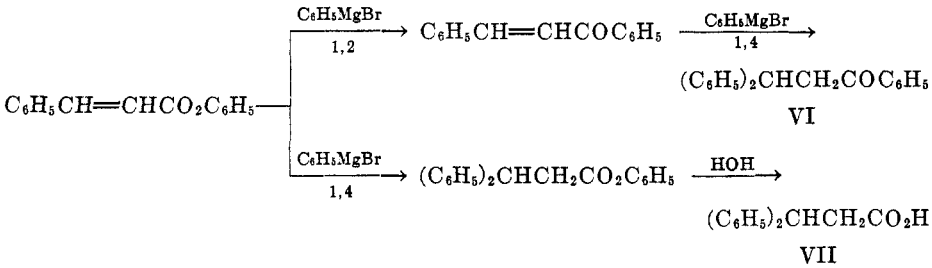
As was expected, cinnamoyl chloride underwent 1,2 addition with sodio acetophenone to form the sodium salt of III which was acylated in the reaction mixture to give dicinnamoylacetophenone (V) in 66% yield.

$$C_6H_5CH{=}CHCOCl \xrightarrow{NaCH_2COC_6H_5} C_6H_5CH{=}CHCOCH_2COC_6H_5 \xrightarrow{NaCH_2COC_6H_5}$$
$$[C_6H_5CH{=}CHCOCHCOC_6H_5]Na \xrightarrow{C_6H_5CH{=}CHCOCl} (C_6H_5CH{=}CHCO)_2CHCOC_6H_5$$

V

The product was shown to be a diacyl derivative rather than a 1,4 addition compound, by synthesis from sodio cinnamoylacetophenone (the sodium salt of III) and cinnamoyl chloride. That it was the C-acyl derivative (V) rather than the O-acyl derivative was indicated by its formation of a copper salt from which it was regenerated.

Reactions with Grignard reagents. Kohler and co-workers (4) have shown that, with phenylmagnesium bromide, ethyl cinnamate exhibits mainly 1,4 addition to form the ester of β,β-diphenylpropionic acid (VII). Some (< 10%) 1,2 addition also occurs under certain conditions to form benzalacetophenone which undergoes 1,4 addition with the Grignard reagent in the reaction mixture to give β,β-diphenylpropiophenone (VI). With methyl cinnamate (4), relatively more 1,2 addition was realized while with phenyl cinnamate (5) almost equal amounts of 1,2 and 1,4 addition were observed. The two courses of reaction with phenyl cinnamate may be represented as



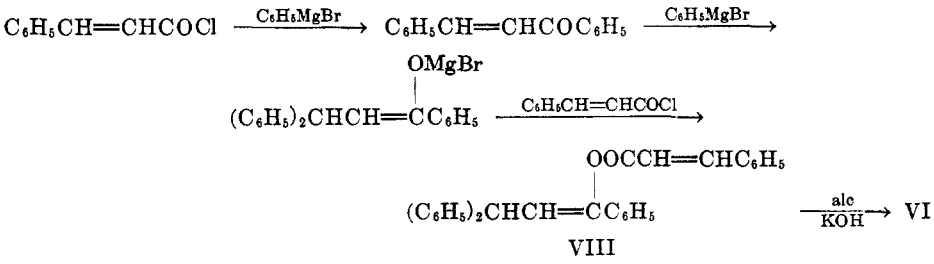
Kohler reported that with *n*-amyl cinnamate (4), less 1,2 addition was observed than with ethyl cinnamate but no yields were given. It has been shown in this laboratory (6) that phenylmagnesium bromide gives apparently only 1,4 addition with *t*-butyl cinnamate, which has a relatively unreactive ester group. In the present work, this has been confirmed the yield being increased from 44% to 76%.

$$C_6H_5CH{=}CHCO_2C(CH_3)_3 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2CHCH_2CO_2C(CH_3)_3$$

Maxim (7, 8) has shown that di-substituted cinnamic amides, for example, N,N-diethyl cinnamamide, gave excellent yields of 1,4 addition product.

$$C_6H_5CH{=}CHCON(C_2H_5)_2 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2CHCH_2CON(C_2H_5)_2$$

The course of addition of phenylmagnesium bromide to cinnamoyl chloride has been difficult to determine. Kohler concluded that both 1,2 and 1,4 addition occurred but he gave no yields. There is no doubt that he realized 1,2 addition since he isolated β,β-diphenylpropiophenone (VI) after treatment of the reaction product with alcoholic potassium hydroxide. He represented the reaction as taking place thus (4)



β,β-Diphenylpropionic acid (VII) also was isolated after hydrolysis. Kohler considered that this acid resulted from direct 1,4 addition of the Grignard reagent to the acid chloride but it might have arisen from 1,4 addition of the reagent to compound VIII which Kohler assumed to be formed from 1,2 addition as represented above. In an experiment with phenylmagnesium bromide and a large excess of cinnamoyl chloride, we isolated only a 1% yield of acid VII. A mixture that was difficult to separate was obtained as the main product; it was not further studied. In this connection it should be pointed out that Nightingale and Wadsworth (9) have shown that cinnamoyl chloride exhibits 1,2 addition with diphenylcadmium to form benzalacetophenone. We have found that diphenylcadmium fails to react with ethyl cinnamate in refluxing ether or benzene, 90% of the ester being recovered unchanged.

In contrast to phenylmagnesium bromide, methylmagnesium iodide appears to give 1,2 addition exclusively; however, the yields have been low. Kohler (4) reported a 27% yield of benzalacetone from methyl cinnamate while Maxim (8) obtained a poor yield of this ketone from N-methyl cinnamanilide. We have been unable to realize appreciable 1,4 addition with methylmagnesium iodide and *t*-butyl cinnamate or N,N-diethyl cinnamamide and with *t*-butylmagnesium chloride and methyl cinnamate. No attempt was made to isolate the 1,2 addition product.

Maxim (7, 8) realized 1,4 addition of ethylmagnesium bromide to di-substituted cinnamamides in excellent yields. However, we have been unable to realize appreciable 1,4 addition with this Grignard reagent and *t*-butyl cinnamate.

Reactions with amino bases. Although cinnamoyl chloride has been reacted with ammonia and various amines, and ethyl cinnamate with ammonia (10, 11) methylamine (11b) and diethylamine (11b), reactions of cinnamic acid derivatives with sodium amide or sodium or magnesium derivatives of amines have apparently not previously been reported.

In the present investigation, sodium amide in liquid ammonia was found to react readily with ethyl cinnamate and even with *t*-butyl cinnamate, by 1,2 addition, to give cinnamamide in 76% and 62% yields, respectively.

$$C_6H_5CH{=}CHCO_2R \xrightarrow{NaNH_2} C_6H_5CH{=}CHCONH_2$$

However, sodium amide reacted with N,N-diethyl cinnamamide to give a 17% yield of the 1,4 addition compound, N,N-diethyl β-aminohydrocinnamamide (IX), a small amount ($< 1\%$) of cinnamamide, and a considerable quantity of a high-boiling unidentified liquid. The reaction mixture immediately assumed a bright red color which changed within one minute to a deep purple. None of the N,N-diethyl cinnamamide was recovered.

$$C_6H_5CH{=}CHCON(C_2H_5)_2 \xrightarrow{NaNH_2} C_6H_5\underset{\displaystyle NH_2}{\underset{|}{C}}HCH_2CON(C_2H_5)_2$$

IX

Sodioaniline, anilinomagnesium bromide, and isobutylaminomagnesium bromide reacted with *t*-butyl cinnamate by 1,2 addition to form the corresponding substituted cinnamamides in yields of 60%, 36%, and 30%, respectively. In the latter two cases, unchanged *t*-butyl cinnamate was recovered in yields of 40% and 43%, respectively. Also, sodiomethylaniline reacted with *t*-butyl cinnamate to give the 1,2 addition product, N-methyl cinnamanilide, in 54% yield. The reaction with the anilino bases may be represented as

$$C_6H_5CH{=}CHCO_2C(CH_3)_3 \xrightarrow[BrMgNHC_6H_5]{NaNHC_6H_5 \text{ or}} C_6H_5CH{=}CHCONHC_6H_5$$

However, diethylaminomagnesium bromide reacted with *t*-butyl cinnamate apparently by 1,4 addition, the primary product reacting further by a Michael type condensation to form (X) in 21% yield; unchanged *t*-butyl cinnamate (33%) was recovered.

$$C_6H_5CH{=}CHCO_2C(CH_3)_3 \xrightarrow{(C_2H_5)_2NMgBr} C_6H_5CH(N(C_2H_5)_2)CH{=}C(OMgBr)OC(CH_3)_3$$

$$C_6H_5CH(N(C_2H_5)_2)CH{=}C(OMgBr)OC(CH_3)_3 \xrightarrow[+ \text{ acid}]{C_6H_5CH{=}CHCO_2C(CH_3)_3} C_6H_5CHCH_2CO_2C(CH_3)_3 \\ CHCO_2C(CH_3)_3 \\ C_6H_5CHN(C_2H_5)_2$$

X

With methyl cinnamate, diethylaminomagnesium bromide reacted by 1,2 addition to give N,N-diethyl cinnamamide in 25% yield.

$$C_6H_5CH{=}CHCO_2CH_3 \xrightarrow{(C_2H_5)_2NMgBr} C_6H_5CH{=}CHCON(C_2H_5)_2$$

In addition methyl cinnamate (28%) was recovered, and there was isolated a product which appeared to be N,N-diethyl β-diethylaminohydrocinnamamide (XI) (11%), resulting from both 1,2 and 1,4 addition. Since N,N-diethylcinnamamide failed to add diethylaminomagnesium bromide under similar conditions, compound XI appears to have resulted from 1,4 addition followed by 1,2 addition.

$$C_6H_5CH(N(C_2H_5)_2)CH_2CON(C_2H_5)_2$$

XI

EXPERIMENTAL[2]

Phenyl cinnamate was prepared from cinnamoyl chloride and phenol by a modification of the general method of preparation of phenyl esters (12), using dimethylaniline in place of pyridine and carbon tetrachloride as solvent. A 74% yield of the ester, m.p. 70–71°, was obtained. After further recrystallizations the ester melted at 75–76° (13); yield, 35%.

t-Butyl cinnamate was prepared from *t*-butyl alcohol and cinnamoyl chloride in the presence of dimethylaniline (14). Since the ester appeared to be contaminated with

[2] Melting points are corrected; boiling points are uncorrected. Microanalyses are by Oakwold Laboratories, Alexandria, Virginia.

cinnamoyl chloride, an ether solution of the product was washed twice with 10% sodium hydroxide. The ether solution was dried over Drierite and the solvent distilled. Fractionation of the residue yielded pure ester (54%), b.p. 122.5–123.5° at 3 mm.

N,N-Diethyl cinnamamide was prepared by a modification of the method of Maxim (15). Cinnamoyl chloride, prepared from 0.6 mole each of cinnamic acid and thionyl chloride, was dissolved in 300 ml. of ether. This solution was added to 87.6 g. (1.2 mole) of diethylamine (b.p. 55.5–56.5°) in 300 ml. of ether in an ice-bath. Water (500 ml.) was added and the ether layer was washed several times with 10% sulfuric acid, then with saturated sodium bicarbonate solution and was finally dried over Drierite. The solvent was distilled and the residue recrystallized from ligroin (70–90°) yielding 101 g. (83%) of colorless needles, m.p. 68–69°. Vorlander and Herrmann (16) report the m.p. as 66° and, Cromwell and Caughlan (17), as 72°. The latter workers describe a good general procedure for the preparation of cinnamamides from cinnamoyl chloride and various secondary amines.

Condensations of ketones with cinnamic acid esters. The ketones were first converted to sodio ketones by means of sodium amide suspended in ether (3). Conversion was assumed to be complete within five to ten minutes. The ester was added to the sodio ketone at room temperature and the resulting mixture was refluxed for one hour. The reaction mixture from phenyl cinnamate and acetone was poured into water and the cinnamoylacetone was precipitated from the aqueous phase with carbon dioxide. In all other cases the reaction mixture was poured onto a mixture of ice and a slight excess of acetic or hydrochloric acid. The ether phase was washed with saturated sodium bicarbonate solution dried over Drierite, and the solvent distilled. The residue from the reaction of ethyl or methyl cinnamate was either fractionated and the direct Michael condensation product isolated or it was hydrolyzed with 10% sodium hydroxide to the acid which was isolated. The residue from the reaction of phenyl cinnamate with acetophenone was dissolved in a minimum amount of methanol and chilled; cinnamoylacetophenone precipitated and was filtered off. The methanol was evaporated from the filtrate and an attempt was made to distill the resulting oil; however, only phenol distilled. The oil remaining in the distilling flask was then refluxed with 10% sodium hydroxide for two and one-half hours yielding 0.38 g. (3%) of an acid, m.p. 146–148° which appeared to be slightly impure β-phenyl-γ-benzoylbutyric acid. Stobbe (2) reported the melting point to be 152–153.5°; in this investigation it was found to be 156–157°.

When the reaction of one equivalent of phenyl cinnamate with two equivalents of sodioacetophenone was carried out, there was obtained from the methanol filtrate a small amount of a white compound which, after recrystallization from alcohol and water, melted at 89–90°. Microanalysis indicated that it was 1,5-dibenzoyl-4-phenylpentanone-2.

Anal. Calc'd for $C_{25}H_{22}O_3$: C, 81.06; H, 5.99.
Found: C, 81.39; H, 5.91.

In each case, some cinnamic acid (5–15%) was obtained on acidification of the sodium bicarbonate wash solution except in the reaction of ethyl cinnamate with pinacolone; here β-phenyl-γ-pivaloylbutyric acid (3%), presumably resulting from hydrolysis of the 1,4 addition product, was obtained.

The yields of the main products using various proportions of the reactants are given in Table II.

Condensation of acetophenone with cinnamoyl chloride. Sodioacetophenone (0.1 mole) was prepared in 180 ml. of ether and dry nitrogen was passed through the suspension while refluxing for one hour to insure complete removal of the ammonia. The ether suspension of the sodio ketone was chilled in a Dry Ice-ether bath (−70°) and cinnamoyl chloride (approximately 0.1 mole, prepared from 14.8 g. of cinnamic acid and 19 ml. of thionyl chloride) dissolved in 75 ml. of ether was added. The resulting yellow suspension was stirred at room temperature for one hour and poured into ice-water containing 5 ml. of glacial acetic acid. A yellow solid separated and was filtered off. The ether phase was dried over Drierite and, after distillation of the solvent, more yellow solid was obtained. The combined product was washed with boiling methanol and dried, yielding 12.5 g. (66%) of dicinnamoyl-

acetophenone, m.p. 181–183°. Two recrystallizations from methanol gave material, m.p. 189–190°.

Anal. Calc'd for $C_{26}H_{20}O_3$: C, 82.08; H, 5.30.
Found: C, 81.62; H, 5.62.

The molecular weight was determined by the freezing point method in benzene; Calc'd for $C_{26}H_{20}O_3$: 380. Found: 382.

The product was further identified by the mixed melting point method using a sample synthesized by reacting equivalent amounts of cinnamoyl chloride with the sodium deriva-

TABLE II

CONDENSATIONS OF KETONES WITH CINNAMIC ACID ESTERS

CINNAMIC ESTER	MOLES	KETONE	MOLES	SODIUM AMIDE (MOLES)	PRODUCT	M.P., °C.	YIELD, %
Ethyl cinnamate	0.1	Acetophenone	0.11	0.11	β-Phenyl-γ-benzoyl-butyric-acid	156–157[a]	66
Ethyl cinnamate	0.1	Acetophenone	0.1	0.2	β-Phenyl-γ-benzoyl-butyric-acid	156–157[a]	37
Ethyl cinnamate	0.1	Acetophenone	0.1	0.01	Ethyl β-phenyl-γ-benzoyl butyrate[b]	61.0–61.5[c, d]	19
Methyl cinnamate	0.1	Acetophenone	0.11	0.11	β-Phenyl-γ-benzoyl-butyric acid	156–157[a]	49
Ethyl cinnamate	0.1	Pinacolone	0.11	0.11	Ethyl β-phenyl-γ-pivaloyl[e] butyrate	b.p. 169–171/5 mm.	64
Phenyl cinnamate	0.05	Acetophenone	0.05	0.1	Cinnamoylacetophenone	108.5–109.5[f]	29
Phenyl cinnamate	0.05	Acetophenone	0.1	0.1	Cinnamoylacetophenone	108.5–109.5[f]	15
Phenyl cinnamate	0.05	Acetone	0.05	0.1	Cinnamoylacetone	83–84[g]	30

[a] Literature (2); 152–153.5°. The oxime melted at 145.5–146.5°; literature (2); 144–144.5°.
[b] Hydrolysis of a sample of the ester gave the acid, m.p. 156–157°.
[c] Literature (19): 59–61°.
[d] B.p. 221–231°/5 mm.
[e] Hydrolysis of a sample of the ester gave the acid, m.p. 124–125°; literature (20): 124°. The amide melted at 132–133°; literature (20): 133°.
[f] Literature (1): 109°.
[g] Literature (1): 83–84°.

tive of cinnamoylacetophenone prepared by means of sodium amide in ether suspension. After refluxing for thirty minutes on the steam-bath, the reaction mixture was poured into water containing acetic acid. The ether phase was washed with water, dried over Drierite and the solvent distilled. The residue was boiled with methanol and filtered giving dicinnamoylacetophenone, m.p. 186–187°, in 40% yield; unreacted cinnamoylacetophenone (26%) was recovered from the methanol filtrate.

The dicinnamoylacetopenone in methanol solution formed a copper derivative (m.p. 247–249°) on treatment with excess saturated copper acetate solution; it was largely recovered on shaking the copper derivative with 20% sulfuric acid.

Reactions of Grignard reagents with cinnamic acid derivatives. To phenylmagnesium bromide, prepared from 5.1 g. (0.21 g. atom) of magnesium and 33 g (0.21 mole) of bromobenzene (b.p. 157°) in 95 ml. of ether, was added 35 g. (0.172 mole) of *t*-butyl cinnamate, fol-

lowed by refluxing on the steam-bath for four hours essentially as described previously (6). A thick yellow precipitate separated. In contrast to the earlier experiment, the reaction mixture was decomposed with ice cold 10% sulfuric acid. The ether phase was washed with saturated sodium bicarbonate and dried over Drierite. The solvent was distilled and the residue steam distilled to remove biphenyl until about 600 ml. of distillate was collected. The mixture in the distilling flask was cooled and extracted with ether. The ether solution was washed with saturated sodium bicarbonate, dried over Drierite, and the solvent distilled. The residue was fractionated through a 10-cm. Vigreux column, yielding 36.5 g. (76%) of *t*-butyl β,β-diphenylpropionate, b.p. 159–160° at 1.75 mm. After one recrystallization from methanol the ester melted at 56.5–57.5°; the reported (6) m.p. is 55.5–55.6°.

In a similar manner, methylmagnesium iodide was reacted with *t*-butyl cinnamate and with N,N-diethyl cinnamamide, and ethylmagnesium bromide was reacted with *t*-butyl cinnamate. The products could not be distilled or crystallized. Only small amounts of impure acids could be isolated after refluxing the products with 48% hydrobromic acid. *t*-Butylmagnesium chloride was reacted with methyl cinnamate but, after refluxing the product with 20% sodium hydroxide, the only product isolated was cinnamic acid (3%).

Reactions of amino bases with cinnamic acid derivatives. The reactions with the sodio amines were carried out by adding an ether solution of the cinnamic acid derivative to a liquid ammonia suspension or solution of sodium amide or of the sodio amine prepared from the appropriate amine and an equivalent of sodium amide in liquid ammonia. After stirring for an appropriate time, excess solid ammonium chloride was added, the ammonia was replaced by ether and the resulting mixture was poured into water. When the product was cinnamamide or cinnamanilide most of it precipitated at this point and was filtered off. The ether phase was extracted several times with 2 *N* hydrochloric acid to remove any amine (see below). The ether solution was then washed with saturated sodium bicarbonate, dried over Drierite and the solvent distilled. Petroleum ether was added to the residue to precipitate amide. After filtering, the petroleum ether was evaporated and the residue fractionally distilled. In the reaction of sodium amide with N,N-diethyl cinnamamide there was obtained a large residue which was refluxed with 10% sodium hydroxide for three hours yielding an oil, b.p. 230–248° at 2 mm., and cinnamic acid (6%).

To the combined hydrochloric acid extracts was added a large excess of potassium carbonate and the amino compound, which separated, was extracted with ether. The ether solution was dried over potassium carbonate, the solvent distilled, and the residue crystallized or fractionated.

The reaction with the aminomagnesium bases was carried out by adding an ether solution of the cinnamic acid derivative to the aminomagnesium base prepared from the appropriate amine and an equivalent of standard ethylmagnesium bromide (18). The mixture was stirred and refluxed for the appropriate time, excess aqueous ammonium chloride was added and the product isolated essentially as described for the sodioamino bases.

The results are summarized in Table III.

SUMMARY

A study has been made of the relative extents of 1,2 and 1,4 additions of certain sodio ketones, Grignard reagents, and metallic amino bases to cinnamic acid derivatives, $C_6H_5CH{=}CHCOX$, as X is varied. In general, with a particular basic reagent, the relative extent of 1,2 addition decreases and that of 1,4 addition increases as X is varied in the following order: Cl, OC_6H_5, OCH_3 or OC_2H_5, $OC(CH_3)_3$, $N(C_2H_5)_2$. The tendency for 1,2 addition appears to be greater and that for 1,4 addition less with sodium amide and related basic reagents than with sodio ketones and phenylmagnesium bromide.

DURHAM, N. C.

TABLE III

REACTIONS OF CINNAMIC ACID DERIVATIVES WITH AMINO BASES

CINNAMIC ACID DERIVATIVE	MOLES	AMINO BASE	MOLES	TIME	PRODUCT	M.P. (°C.)	YIELD, %
Ethyl cinnamate	0.1	Sodium amide	0.2	30 min.	Cinnamamide	147–148[a]	76
t-Butyl cinnamate	0.05	Sodium amide	0.1	1 hr.	Cinnamamide	149–150[a]	62
t-Butyl cinnamate	0.05	Sodium amide	0.1	5 min.	Cinnamamide	146–147[a]	27
N,N-Diethyl cinnamamide	0.15	Sodium amide	0.15	1 hr.	N,N-Diethyl-β-aminohydrocinnamamide[b]	b.p. 160–163/2 mm.	17[c, d]
t-Butyl cinnamate	0.05	Sodioaniline	0.05	30 min.	Cinnamanilide	150–151[e]	60
t-Butyl cinnamate	0.05	Anilinomagnesium bromide	0.05	2 hrs.	Cinnamanilide	153.5[e]–154.5	36[f]
t-Butyl cinnamate	0.1	Isobutylaminomagnesium bromide	0.1	3 hrs.	N-Isobutyl cinnamamide	110–111[g]	30[h]
t-Butyl cinnamate	0.1	Sodiomethylaniline	0.1	1 hr.	N-Methyl cinnamanilide[i]	b.p. 192/2 mm.[j]	54
t-Butyl cinnamate	0.08	Diethylaminomagnesium bromide	0.08	10 min.	Di-*t*-butyl ester (X)[k]	81–82	21[l]
Methyl cinnamate	0.1	Diethylaminomagnesium bromide	0.1	10 min.	N,N-Diethyl cinnamamide	68–69[m]	24[n, o]

[a] Literature (21): 147°; identified by the mixed melting point method. [b] The picrate melted at 210–211°. *Anal.* Calc'd for $C_{19}H_{23}N_5O_8$: C, 50.78; H, 5.16; N, 15.59. Found: C, 50.76; H, 5.58; N, 15.40. [c] A trace of cinnamamide also distilled and solidified in the condenser. [d] A run using two equivalents of sodium amide to one of N,N-diethyl cinnamamide gave the same result. [e] Literature (21): 150°. [f] *t*-Butyl cinnamate (40%) was recovered. [g] Literature (22): 114°; the mixed melting point with a sample of N-isobutyl cinnamamide (m.p. 111–112°), prepared from cinnamoyl chloride and isobutylamine, was 110.5–111.5°. [h] *t*-Butyl cinnamate (43%) was recovered. [i] *Anal.* Calc'd for $C_{16}H_{15}NO$: N, 5.90; Found: N, 6.14. [j] Literature (8): 231°/15 mm. [k] *Anal.* Calc'd for $C_{30}H_{43}NO_4$: C, 74.80; H, 9.00; N, 2.91. Found: C, 74.66; H, 8.81; N, 3.07. [l] *t*-Butyl cinnamate (33%) was recovered. [m] Literature (16): 66°. [n] *t*-Butyl cinnamate (28%) was recovered. [o] There was also obtained a compound which was presumably N,N-diethyl β-diethylaminohydrocinnamamide, b.p. 162–168°/2 mm., in 11% yield (based on methyl cinnamate). The methiodide melted at 168–169°. *Anal.* Calc'd for $C_{18}H_{31}IN_2O$: N, 6.70; I, 30.34. Found: N, 6.53; I, 29.87.

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