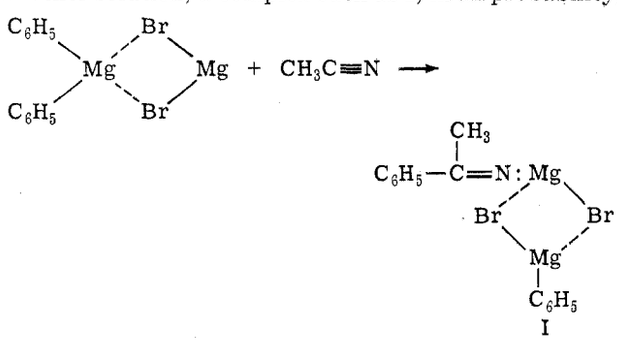
TABLE I
KETONES PREPARED FROM REACTION OF GRIGNARD REAGENT WITH NITRILES

Nitrile	Grignard reagent	Ketone	% yield[a]	Reported yield[b]
Acetonitrile	Phenylmagnesium bromide	Acetophenone	42 (68)[c]	37–45 (70)[d]
Acetonitrile	3,5-Dibromophenylmagnesium bromide	3,5-Dibromoacetophenone	1 (52)[e]	
Acetonitrile	*n*-Pentylmagnesium bromide	2-Heptanone	44[c]	14
Acetonitrile	Benzylmagnesium chloride	Methylbenzyl ketone	34[c]	16
Acetonitrile	*n*-Octylmagnesium bromide	2-Decanone	49[c]	
Propionitrile	Phenylmagnesium bromide	Propiophenone	94	80–91
Pivalonitrile	Phenylmagnesium bromide	Pivalophenone	90	72
Trifluoroacetonitrile	Phenylmagnesium bromide	α,α,α-Trifluoroacetophenone	82	
Trideuterioacetonitrile	Phenylmagnesium bromide	α,α,α-Trideuterioacetophenone	65	

[a] Yield based on product isolated. Diethyl ether used as solvent except where noted. [b] M. S. Karasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, New York, N. Y., 1954, p 793. [c] Benzene used as solvent. [d] Higher yield of 70% obtained when Grignard reagent used in large excess. [e] Benzene used as solvent and trimethyl orthoacetate used instead of acetonitrile.

showed 46.8% monodeuteriobenzene. This indicated that 53.2% benzene was being derived from a source other than the "active" hydrogen atoms of acetonitrile. A significant isotope effect was observed because an increase in ketone yield from 42% to 65% was found.

If one assumes that the Grignard reagent is dimeric in ether solution, a complex such as I, in all probability,



would be formed. Hydrolysis of I should also be a source of benzene. In the first hydrolysis experiment, deuterium oxide was added to react with unreacted Grignard reagent in the complex, followed by addition of hydrochloric acid to complete the hydrolysis. Analysis of the benzene produced gave only 2.4% monodeuteriobenzene. This observation was attributed to the fact that I is ether insoluble and forms a "ball-shaped" conglomerate, allowing only the outer surface to come in contact with the D_2O.

In order that unreacted phenylmagnesium bromide in I be permitted to react completely with a labeled compound such as D_2O, complete hydrolysis would be essential. For this purpose, deuterium chloride in deuterium oxide was used as a means for hydrolysis of I. Mass spectrometric analysis of the benzene fraction gave 51.8% monodeuteriobenzene.

It is of interest to note that a change in solvent from ether to benzene gives an increase in yield from 42% to ~70% acetophenone.

Experimental Section[7]

General Procedure for Synthesis of Ketones.—The appropriate Grignard reagent was prepared from reaction of the halide (0.1 mol) with magnesium (0.1 g-atom) in anhydrous diethyl ether (100 ml). Precautions were taken to exclude moisture from the reaction flasks. In some cases, benzene was added dropwise to the freshly prepared Grignard reagent, and the ether removed by distillation prior to addition of the nitrile. The nitrile (0.1 mol) was added dropwise over a period of approximately 15 min. Most of the reactions are quite exothermic. After continuous stirring and refluxing for 2 hr, the mixture was hydrolyzed with hydrochloric acid and ice. Extraction with ether or benzene, followed by vacuum distillation, gave the ketone.

Labeling Experiments.—Substitution of trideuterioacetonitrile for acetonitrile yielded benzene (25 g, 32%) containing 46.8% monodeuteriobenzene. Mass spectrometric analysis of the resulting ketone showed no deuterium atoms in the $C_6H_5CO^+$ and $C_6H_5^+$ ions, but that the labeling is limited to the methyl group. Overall, 80.5% of the methyl hydrogens are deuterium atoms, which is very close to the theoretical, 83%.

Benzene (26 g, 33%) obtained as a product from reaction of acetonitrile and phenylmagnesium bromide followed by attempted hydrolysis with D_2O showed only 2.4% labeling. Benzene (25 g, 32%) obtained from the same reactants, but followed by hydrolysis with 20% DCl in D_2O, showed 51.8% labeling.

Registry No.—Phenylmagnesium bromide, 100-58-3; acetonitrile, 75-05-8; acetophenone, 98-86-2; 3,5-dibromoacetophenone, 14401-73-1; 2-heptanone, 110-43-0; methyl benzyl ketone, 103-79-7; 2-decanone, 693-54-9; propiophenone, 93-55-0; pivalophenone, 938-16-9; α,α,α-trifluoroacetophenone, 434-45-7; α,α,α-trideuterioacetophenone, 17537-31-4.

Acknowledgment.—The authors are grateful to Dr. Seymour Meyerson, Research and Development, American Oil Company, Whiting, Indiana, for assistance in the procurement and interpretation of mass spectral data on the labeled compounds.

(7) Isotopic compositions of the benzene and acetophenone samples obtained from the labeling reactions were measured at reduced ionizing voltage and 70 eV, respectively, on a Consolidated 21-102/103c mass spectrometer. All deuterium labeled compounds were obtained from Diaprep, Inc., Atlanta, Georgia, and had 99.5% minimum isotopic purities.

2*H*-1,2,3-Triazoles from the Ethyl Nitrocinnamates[1]

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The facile synthesis of 2*H*-1,2,3-triazoles by the addition of azide ion to activated acetylenes (eq 1) is not

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TABLE I

THE REACTIONS OF THREE ETHYL NITROCINNAMATES WITH SODIUM AZIDE[a]

Ethyl nitrocinnamate	Solvent[b] (additive)	Temp, °C	Time, hr	Triazole[c] yield,[i] % (I)	Azo[d] yield,[i] % (II)	Recovered[g] cinnamate, % (III)
Para	DMF	75	5	29	Trace	54
Para	DMF	120	2	64	4.7	5.8
Para	DMAC	120	2	55	3.6	
Para	DMSO	120	2	62	4.5	
Meta	DMSO	120	2	57	*e*	39
Meta	DMAC	120	14	48	*e*	
Meta	DMSO	150	2	52	*e*	
Ortho	DMF	120	2	13	*f*	
Para	($C_6H_5NO_2$)	90–110	3.5	52		25
Para	(m-$C_6H_4(NO_2)_2$)	120	2	0		59
Para	(p-$(CH_3)_2NC_6H_4NO$)	110	1	31		37
Para	(Dry air)[h]	120	2	23		58
Para	(SeO_2)	120	1	50		34

[a] The reactions were generally carried out on a 1-g scale under nitrogen, except as indicated. [b] DMF, dimethylformamide; DMAC, dimethylacetamide; DMSO, dimethyl sulfoxide. Where no additive is indicated none was used. The standard solvent with additives was DMF (not indicated). When 1-chloro-2,4-dinitrobenzene or sulfur powder were the additives (1–2 hr at 120°), colored gums were obtained. [c] Nitrophenyl-5-carboethoxy-1,2,3-triazole. [d] Ethyl p,p'-azocinnamate. Traces of azoxy compound were detected in mass spectrum. [e] Unknown brown gummy mixture. [f] Unknown red gummy mixture. [g] A blank means that recovery of material either was not attempted or was not successful. [h] Dry air was continuously bubbled through the reaction mixture. [i] Yields are based on purified compounds.

$$RC{\equiv}CR' \xrightarrow[2.\ H_3O^+]{1.\ NaN_3,\ DMF} \underset{\mathbf{T}}{\text{1,2,3-triazole}} \qquad (1)$$

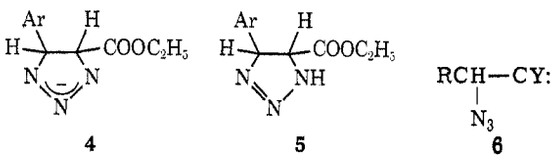
yet well known.[2,3] Having developed process 1 in great detail,[1] we believed that activated alkenes might also have synthetic possibilities. Although styrene[2] and ethyl maleate, quinone, and tetracyanoethylene did not give isolable products, the three ethyl nitrocinnamates (**1**) led, unexpectedly, to 1,2,3-triazoles (**2**), and in one case, also to ethyl azocinnamate (*p*-**3**).

The results of the investigation of process 2 are given in Table I. Among the aprotic solvents, DMF, DMAC, and DMSO, none showed any marked advantage. Our usual reaction temperatures were 100–150°, but temperatures above 150° led to decreased yields of **2**. Note that, if the reaction proceeded according to eq 2,

$$\underset{\mathbf{1}\ (o,\ m,\ p)}{O_2NC_6H_4CH{=}CHCOOC_2H_5} \xrightarrow[2.\ H_3O^+]{1.\ NaN_3,\ DMF} \underset{\mathbf{2}\ (o,\ m,\ p)}{O_2NC_6H_4\text{-triazole-}COOC_2H_5} + \underset{p\text{-}\mathbf{3}}{(=NC_6H_4CH{=}CHCOOC_2H_5)_2} \qquad (2)$$

the stoichiometry (6 **1** → 4 **2**) set 66.7% as the theoretical maximum possible yield for **2**. Although this limit was approached for the meta and para isomers, the ortho yield did not get close, presumably because competing processes intervened (Table I).

As a working hypothesis, we considered that azide ion adds to **1** to give an open or closed anion (**4**), or triazoline (**5**). Now, triazolines may be oxidized,[4] may eliminate 5-H and 4-X to form triazoles, or may shed nitrogen and form aziridines, but they do not usually react with oxygen or the nitro function under our reaction conditions.[4,5] The fact that we were able to isolate **2** and *p*-**3** indicates that a redox process occurred, involving the transfer of hydride from **4**, **5**, or a



4 **5** **6**

related species to some acceptor; it seems probable but is by no means certain yet that the oxidant is the nitro group (**1**) and/or other possible nitrogen precursors (hydroxylamino, nitroso, and azoxy)[6] to *p*-**3**. Nevertheless, our efforts to understand the detailed course of reaction 2 and to increase the yield of triazole by facilitating the oxidation of the intermediates with additives were negative or inconclusive (Table I). Potential oxidants such as air and dinitrobenzene turned out to be inhibitors and led to decreased yields of *p*-**2**.

A number of syntheses of triazoles from activated alkenes are on record. In one group of these, *e.g.*, from 5-nitro-2-oxopyrimidine,[7] 1,2-dicyanoethylene,[8] 1,4-dicyanobutadiene,[8] β,β'-dicyanostyrene,[8] and possibly β-nitrostyrene,[8] *there is a net displacement of X* from RCH=CR′X and the resulting triazole is the one formally derived from RC≡CR′, according to eq 1. Following azide addition to the double bond, the timing of the departure of X^-, ring closure, and proton transfer from carbon to nitrogen is unclear,[7,8] but in at least two possibly related cases a stable intermediate, *i.e.*, 2-

(2) A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR*, **158**, 408 (1964).
(3) F. P. Woerner and H. Reimlinger, *Chem. Ber.*, **103**, 1908 (1970).
(4) G. Caronna and S. Palazzo, *Gazz. Chim. Ital.*, **82**, 292 (1952).
(5) (a) P. Scheiner in "Selective Organic Transformations," Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1970, p 327; P. Scheiner, *Tetrahedron*, **24**, 2757 (1968); (b) R. Huisgen, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 1138 (1965).
(6) P. Buck, *Angew. Chem., Int. Ed. Engl.*, **8**, 120 (1969).
(7) H. U. Blank, I. Wemper, and J. J. Fox, *J. Org. Chem.*, **35**, 1131 (1970).
(8) (a) N. S. Zefirov and N. K. Chapovskaya, *Zh. Org. Khim.*, **6**, 2596 (1970); (b) N. S. Zefirov, N. K. Chapovskaya, and V. V. Kolesnikov, *Chem. Commun.*, 1001 (1971).

tosylvinyl azide or 2-benzoylvinyl azide, forms and slowly rearranges to **T** in the presence of base (N_3^-) in aprotic solvent.[9]

In a second group of syntheses, X may or may not be lost in the reaction, but here *a redox process or some other deep-seated changes* may occur: three β-nitrostyrenes yield 4-aryltriazoles and *sym*-triarylbenzenes;[8] β-cyanostyrene yields 4-phenyltriazole and 4-cyano-5-phenyltriazole;[8] three β-aroylethylene sulfonates yield corresponding 4-aroyltriazoles and phenylacylmethionic acids [p-$XC_6C_4COCH_2CH(SO_3^-)_2$];[10] three nitrocinnamates yield 4-(nitrophenyl), 5-carboethoxytriazole (eq 2). In his work, Zefirov, *et al.*, has pointed out that neither alkynes nor vinyl azides are necessary intermediates in these reactions; they suggest **4**, **5**, or the carbene **6** as possible precursors of the triazole.[8] However, even superficial consideration of these four examples discloses probable differences in the stoichiometry of the processes, in the nature of the coproducts, and in their detailed mechanisms. The formation of 4-cyano-5-phenyltriazole and the nitrophenyl-5-carboethoxytriazoles clearly require a hydride transfer; in the remaining reactions the cyano and sulfonate groups appear to be exchanged in "disproportionations." What does appear to connect all of the examples of this group and what does not seem to have been identified and emphasized previously is that redox processes are occurring. Admittedly, critical mechanistic information about them is still lacking. Since there would be obvious advantages in going to triazole directly from an alkene rather than from an alkyne made from the same alkene, there are practical and theoretical incentives for unravelling the mechanism(s) of these syntheses.

Experimental Section

Syntheses of Nitrophenyl-5-carboethoxy-1,2,3-triazoles from Nitrocinnamates.—The following preparative method was general, but the details of separation of components apply specifically to the para ester rather than to the ortho and meta compounds, for which the coproducts of the derived triazole were not identified. A summary of this work is given in Table I.

To a stirred suspension of sodium azide in an aprotic solvent,[11] blanketed by a stream of dry N_2, was added dropwise a solution of ethyl 4-nitrocinnamate in the same solvent at 75–150° over 30 min. The solution was kept at this temperature for 2–14 hr, when it turned green-brown, and then evaporated to dryness at *ca.* 60° under reduced pressure (2–3 mm). The residue was taken up in 50% aqueous methanol. Materials insoluble in the aqueous methanol were filtered off, washed with water, redissolved, and reprecipitated from acetone–water; these may consist of ethyl nitrocinnamate, ethyl azocinnamate, and possibly ethyl azoxycinnamate. Further separation was attempted by column chromatography on alumina with chloroform and chloroform–acetone as eluting solvents. Unreacted ethyl nitrocinnamate appeared in the first eluates. When present, the azo compound appeared next (trace amounts of azoxy compound mixed in with the azo compound were sometimes detected by mass spectroscopy, parent peak m/e 394). The aqueous solution, from which the mixture of the azo compound and the unchanged reactant were separated, was neutralized with 10% hydrochloric acid. An orange solid gradually precipitated. This was filtered off, washed with water, dried under reduced pressure, and reprecipitated from ethanol–water. The light orange solid was further purified by chromatography on silica gel with benzene, ether, and methanol as eluents, and identified as 4-nitrophenyl-5-carboethoxytriazole.

Ethyl p,p'-Azocinnamate (p-3).—This compound had mp 150–153° dec; nmr ($CDCl_3$) τ 8.65 (t, J = 7.3 Hz, 6 H), 5.69 (q, J = 7.3 Hz, 4 H), 3.51 (d, J = 16.2 Hz, 2 H), 2.27 (d, J = 16.2 Hz, 2 H), 2.32 (d, J = 8.7 Hz, 4 H), 2.05 (d, J = 8.7 Hz, 4 H); ir (Nujol) 1704, 1630 cm^{-1}; uv (ethanol) λ_{max} 366 nm (ε 52,300); mass spectrum m/e 378 (P^+), 333, 203, 181, 175, 147.

Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86. Found: C, 69.89; H, 5.82.

4-(p-Nitrophenyl)-5-carboethoxy-1,2,3-triazole.—This material had mp 170–171°; nmr (CD_3COCD_3) τ 8.66 (t, J = 7.1 Hz, 3 H), 5.60 (q, J = 7.1 Hz, 2 H), 1.72 (s and m, 4 H); ir (KBr) 3120, 1720, 1605, 1525 cm^{-1}; uv (ethanol) λ_{max} 290 nm (ε 12,400).

Anal. Calcd for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.90. Found: C, 50.52; H, 4.09.

4-(m-Nitrophenyl)-5-carboethoxy-1,2,3-triazole.—This compound had mp 105–106°; nmr (acetone) τ 8.57 (t, J = 7.2 Hz, 3 H), 5.48 (q, J = 7.2 Hz, 2 H), 2.34 (m, 1 H), 1.71 (m, 2 H), 1.10 (t, J = 1.8 Hz, 1 H); ir (KBr) 3100, 1725, 1540 cm^{-1}; uv (ethanol) λ 249 nm (ε 16,700).

Anal. Calcd for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.90. Found: C, 49.83; H, 3.90. In this reaction, the azo compound was presumed to be a coproduct.

4-(o-Nitrophenyl)-5-carboethoxy-1,2,3-triazole.—This light red triazole had mp 27–41°; nmr ($CDCl_3$) τ 8.82 (t, J = 7.1 Hz, 3 H), 5.72 (q, J = 7.1 Hz, 2 H), 2.33 (m, 3 H), 1.90 (m, 1 H); ir (liquid) 3160, 1715, 1520, 1440 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.90. Found: C, 50.14; H, 3.78.

Registry No.—p-2, 35307-27-8; m-2, 35378-21-3; o-2, 35307-28-9; p-3, 35340-31-9.

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(11) *E.g.*, DMF, DMAC, or DMSO.

Nuclear Magnetic Resonance and Infrared Studies on the Tautomerism of 1-Ethyl-3-(3′-dimethylaminopropyl)-carbodiimide[1a]

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Chemotherapy trials performed during the past year have demonstrated that 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (**1**), when administered as a saline solution of its hydrochloride salt, exerts a carcinostatic effect on transplanted tumors in mice.[2] Sheehan, *et al.*,[3] have suggested from ir studies that protonation of the tertiary amine of the carbodiimide **1** may lead to the formation of the tautomeric, reduced pyrimidines 2-ethylamino-3,3-dimethyl-3,4,5,6-tetrahydropyrimidine chloride (**4**) and/or 2-ethylimino-3,3-dimethylper-

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