corresponding fully aromatic fluoranthene derivatives. In this manner were prepared fluoranthene, 7-methylfluoranthene, 8-methylfluoranthene, 8,9-dimethylfluoranthene and ethyl 10-methyl-7-fluoranthenecarboxylate.

LOS ANGELES, CALIF. RECEIVED APRIL 3, 1950

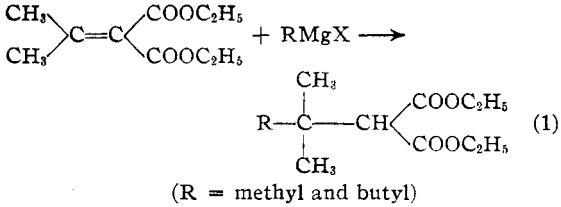
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Synthesis of Ethyl *t*-Alkylcyanoacetates

BY ELLIOT R. ALEXANDER, JOHN D. MCCOLLUM AND DONALD E. PAUL

In general, the preparation of substituted acetoacetic, malonic, or cyanoacetic esters by an alkylation procedure is suitable only for the introduction of primary or secondary alkyl groups. Under the alkaline conditions employed, *t*-alkyl halides readily dehydrohalogenate to form alkenes. Ethyl *t*-butylcyanoacetate, for example, appears to be unknown.

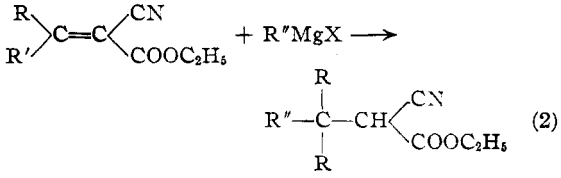
Recently, however, the synthesis of ethyl *t*-alkylmalonates has been reported[1] by the conjugate addition of Grignard reagents to ethyl isopropylidenemalonate (equation 1). It was the object of this work to explore the scope and limitations of this reaction in the synthesis of



(1)

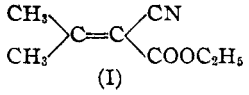
(R = methyl and butyl)

ethyl *t*-alkylcyanoacetates (equation 2).

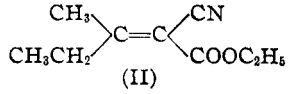


(2)

In Table I are summarized the ethyl *t*-alkylcyanoacetates which were prepared by the conjugate addition of Grignard reagents to ethyl 1-methylethylidenecyanoacetate (I) and ethyl 1-methylpropylidenecyanoacetate (II). With ethyl 1-methylethylidenecyanoacetate the method ap-



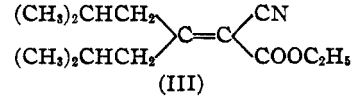
(I)



(II)

pears to be quite general for *n*-alkyl or phenyl groups and the yields of pure *t*-alkylcyanoacetates range from 42–75%. Experiments were also carried out with isopropylmagnesium bromide and *t*-butylmagnesium chloride, but in each case the reaction led to a mixture of products which could not be separated by distillation through an eight-inch electrically heated column packed with glass helices. It is interesting that in the one case that was studied, namely, the addition of methylmagnesium iodide to ethyl 1-methylethylidenecyanoacetate, there appeared to be no tendency for a second molecule of Grignard reagent to add either to the nitrile group or to the carbethoxyl group. Thus, when a 10 molar excess of methylmagnesium iodide was employed and the reaction mixture was allowed to stir overnight, the yield of ethyl *t*-butylcyanoacetate was the same (57%) as that obtained by using a 1.2 molar excess of methylmagnesium iodide. With the isopropyl or *t*-butyl Grignard reagents, however, (where the reaction failed) infrared analysis showed the presence of hydroxyl groups in the mixture of products which was obtained.

Just as the reaction fails with the secondary or tertiary Grignard reagents which were employed, there is a limiting unsaturated ester for the synthesis. The reaction between ethyl 1-methylpropylidene cyanoacetate and methylmagnesium iodide proceeded normally (Table I) and again treatment with isopropylmagnesium bromide led to inseparable mixtures. With ethyl 1-isobutyl - 3 - methylbutylidenecyanoacetate (III), however, mixtures were obtained even from



(III)

methylmagnesium iodide and benzylmagnesium chloride.

Acknowledgment.—We are indebted to Miss Theta Spoor, Miss Rachel Kopel and Miss Emily Davis for the microanalyses which are reported in this paper.

Experimental[2]

Ethyl Alkylidenecyanoacetates.—The unsaturated esters which are mentioned in this paper were prepared by the method of Cope and Hofmann[3] which is based upon a Knoevenagel condensation of ethyl cyanoacetate with the appropriate ketone. Before use, all of the esters were distilled to constant refractive index through an eight-inch electrically heated column packed with glass helices.

Ethyl *t*-Butylcyanoacetate.—The experiments summarized in Table I were carried out according to the following procedure. It is illustrated here with the preparation of ethyl *t*-butylcyanoacetate.

In a dry 500-ml. three-necked flask fitted with a stirrer, an addition funnel, and a condenser protected from the

(1) Wideqvist, *Arkiv. Kemi, Mineral. Geol.*, **B22**, No. 4 (1946); *C. A.* **41**, 1615 (1947).

(2) All melting points and boiling points are uncorrected.

(3) Cope and Hofmann, THIS JOURNAL, **63**, 3457 (1941).

TABLE I

ETHYL *t*-ALKYLCYANOACETATES, $RCH(CN)COOC_2H_5$

	t-Alkyl group, R	Halide used in preparation of Grignard reagent	Yield, %	B. p. °C.	B. p. mm.
	(A) From Ethyl 1-Methylethylidenecyanoacetate				
1	*t*-Butyl	Methyl iodide	75	88	5
2	1,1-Dimethylpentyl	*n*-Butyl bromide	42	109	2
3	1,1-Dimethyl-2-phenylethyl	Benzyl chloride	49	142–143	0.4
4	1,1-Dimethylbenzyl	Bromobenzene	60	155	0.5
	(B) From Ethyl 1-Methylpropylidenecyanoacetate				
5	1,1-Dimethylpropyl	Methyl iodide	41	75–76	0.9

$n^{20}D$	d^{20}_4	Molecular refraction Calcd.	Found	Formula	Carbon, % Calcd.	Found	Hydrogen Calcd.	Found
		(A) From Ethyl 1-Methylethylidenecyanoacetate						
1.4278	0.9629	45.23	45.26	$C_9H_{15}O_2N$	63.88	64.17	8.94	9.07
1.4392	0.9430	59.08	59.07	$C_{12}H_{21}O_2N$	68.20	68.47	10.02	10.26
1.5032	1.0432	69.24	69.67	$C_{15}H_{19}O_2N$	73.44	73.57	7.81	8.08
1.5062	1.0570	64.72	65.15	$C_{14}H_{17}O_2N$	72.70	72.93	7.41	7.50
		(B) From Ethyl 1-Methylpropylidenecyanoacetate						
1.4369	0.9633	49.87	49.91	$C_{10}H_{17}O_2N$	65.55	65.39	9.34	9.42

atmosphere by a calcium chloride tube, was prepared a Grignard solution from 6.8 g. (0.28 mole) of magnesium, 39.9 g. (0.28 mole) of methyl iodide, and 60 ml. of ether. To this solution was then added 40.0 g. (0.234 mole) of ethyl isopropylidenecyanoacetate at such a rate that the reaction mixture refluxed gently. After addition was complete, the two-phase system was heated gently on the steam-bath, with stirring, for one hour. The complex was then cooled and poured onto a mixture of ice and 15% aqueous ammonium chloride solution. After separating the organic layer and extracting the aqueous layer with ether, the organic portion and the ether extracts were combined, washed with water, and dried over anhydrous magnesium sulfate. The excess ether was then removed *in vacuo* and the residue was distilled through an eight inch electrically heated column packed with glass helices.

Infrared analysis showed nitrile and ester-carbonyl groups, but there was no indication of carbon–carbon double bonds or hydroxyl groups.[4] The ester gave negative tests with sodium hypoiodite, acetyl chloride, 2,4-dinitrophenylhydrazine and ferric chloride. The odor of ammonia could be detected when it was heated with sodium hydroxide in diethylene glycol solution. Hydrogen bromide was evolved on treatment with bromine in carbon tetrachloride solution. Saponification gave *t*-butylmalonic acid, m. p. 149.5–151°[1] and conversion of the volatile portion of the saponification mixture to a 3,5-dinitrobenzoate gave a product which melted at 90° and showed no depression when admixed with ethyl 3,5-dinitrobenzoate.

(4) We are indebted to Dr. Foil A. Miller, Mrs. J. L. Johnson, and Miss Elizabeth Peterson for the determination and interpretation of these curves.

Summary

The conjugate addition of phenyl and primary Grignard reagents to ethyl 1-methylethylidenecyanoacetate constitutes a general method for the synthesis of several ethyl *t*-alkylcyanoacetates. The yields are 42–75%. An investigation of the scope and limitations of the reaction has been carried out.

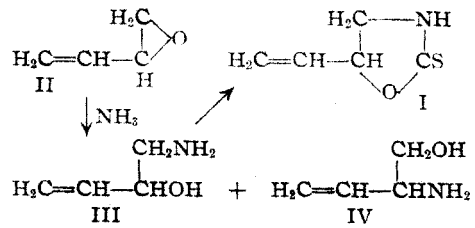
URBANA, ILLINOIS RECEIVED APRIL 20, 1950

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of the Natural Antithyroid Factor *l*-5-Vinyl-2-thioöxazolidone[1]

BY MARTIN G. ETTLINGER[2]

The antithyroid factor of turnip root and seeds of numerous *Brassicae*, including cabbage, turnip and rape, has been isolated and proved to be *l*-5-vinyl-2-thioöxazolidone (I).[3] Ingestion of the substance may cause simple goiter.[4,5] The present paper contains a description of synthesis of the naturally occurring form of I.



The starting material, butadiene-1,2-oxide[6] (II), furnished on ammonolysis 1-amino-3-buten-

(1) **Preliminary communication**: Astwood, Greer and Ettlinger, *Science*, **109**, 631 (1949).

(2) **Member of the Society of Fellows, Harvard University.**

(3) **Astwood**, Greer and Ettlinger, *J. Biol. Chem.*, **181**, 121 (1949).

(4) **Astwood**, *Ann. Internal Med.*, **30**, 1087 (1949).

(5) **Greer, Ettlinger and Astwood**, *J. Clin. Endocrinol.*, **11**, 1069 (1949); *Trans. Am. Goiter Assoc.*, 55 (1949).

(6) **Pariselle**, *Ann. chim.*, [8] **24**, 315 (1911); **Kadesch**, THIS JOURNAL, **68**, 41 (1946).