[CONTRIBUTION FROM THE ROHM AND HAAS COMPANY, REDSTONE ARSENAL RESEARCH DIVISION]

Alkaline Nitration. II. The Nitration of Active Methylene Compounds with Acetone Cyanohydrin Nitrate[1]

BY WILLIAM D. EMMONS AND JEREMIAH P. FREEMAN

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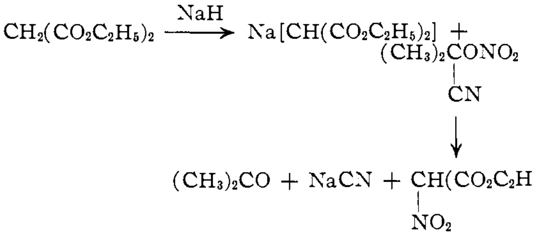
The nitration of a variety of active methylene compounds (in the form of their sodio derivatives) has been effected by the use of acetone cyanohydrin nitrate. Using this reaction a new and general synthesis of α-nitro esters has been established. The mechanism of this reaction is discussed.

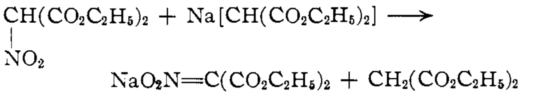
Acetone cyanohydrin nitrate has been found to be a singularly effective reagent for the nitration of active methylene compounds under alkaline conditions. It has been possible to nitrate malonic and acetoacetic esters, and arylacetonitriles in good yields. Acetone cyanohydrin nitrate thus constitutes a general reagent available for alkaline nitration and accordingly should find considerable use in organic synthesis.

Nitration by means of a nitrate ester in the presence of added base has found only limited use as a synthetic tool up to this time. In the pioneer work in this field Wislicenus and his co-workers showed that arylacetonitriles such as phenylacetonitrile[2] or α-naphthylacetonitrile,[3] arylacetic esters[2] and fluorene[4] could be nitrated, often in excellent yields. In all cases these workers used ethyl nitrate in the presence of sodium ethoxide. It was explicitly stated[2,3] that the reaction was not a general one and that nitroacetic esters, for example, could not be prepared in this way. Later the reaction was extended to include the nitration of cyclic ketones although relatively poor yields (20–30%) of the desired products were obtained.[5,6]

The high order of reactivity displayed by acetone cyanohydrin nitrate in the nitration of amines[7] suggested that it would also prove to be a unique reagent for the nitration of active methylene compounds, and indeed this has been found to be true. The nitration of diethyl malonate with acetone cyanohydrin nitrate was examined in detail. It was discovered at the outset that a non-hydroxylic solvent was required as metal alkoxides rapidly destroyed the nitrate ester.[8] While both benzene and di-*n*-butyl ether proved to be satisfactory solvents for the reaction, tetrahydrofuran was the solvent of choice as the sodio derivatives of the active methylene compounds were soluble in it. Sodium hydride was used as the base and the nitrate ester was added to the preformed salt. An examination of equation 2 shows that either an excess of the added base or of sodio malonic ester is necessary in order to ensure good yields of diethyl nitromalonate since the equilibrium (2) favors the formation of the nitronate salt thus destroying an equivalent of sodio malonic ester. An excess of sodium hydride could not be used, however, as it degraded the nitromalonic ester to ethyl nitroacetate. When a threefold excess of sodio malonic ester was used, diethyl nitromalonate was obtained in 45% yield.

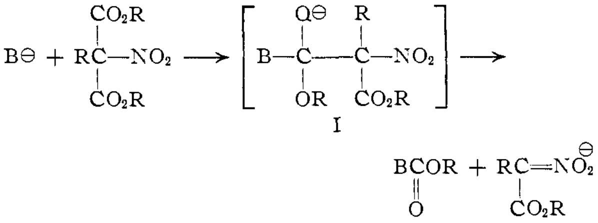


$$CH_2(CO_2C_2H_5)_2 \xrightarrow{NaH} Na[CH(CO_2C_2H_5)_2] + (CH_3)_2\underset{\underset{CN}{|}}{C}ONO_2 \longrightarrow (CH_3)_2CO + NaCN + \underset{\underset{NO_2}{|}}{C}H(CO_2C_2H_5)_2 \quad (1)$$



$$\underset{\underset{NO_2}{|}}{C}H(CO_2C_2H_5)_2 + Na[CH(CO_2C_2H_5)_2] \longrightarrow NaO_2N{=}C(CO_2C_2H_5)_2 + CH_2(CO_2C_2H_5)_2 \quad (2)$$

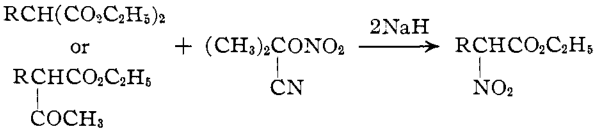
The alkaline degradation of nitromalonic esters has been noted previously.[9,10] Ethyl phenylnitroacetate is also decarbethoxylated by ethoxide ion[2]; diethyl carbonate was isolated from this reaction. In the case under investigation hydride ion presumably is the base responsible for the degradation. Tricarbethoxymethane, the product which would result if sodio malonic ester were the active base, was never found in the reaction mixture. The superiority of the nitronate anion over alkoxide ion as a leaving group from the intermediate I probably accounts for the facility with which this reaction occurs.



$$B^{\ominus} + R\overset{\overset{CO_2R}{|}}{\underset{\underset{CO_2R}{|}}{C}}{-}NO_2 \longrightarrow \left[B{-}\overset{\overset{O^{\ominus}}{|}}{\underset{\underset{OR}{|}}{C}}{-}\overset{\overset{R}{|}}{\underset{\underset{CO_2R}{|}}{C}}{-}NO_2\right] \longrightarrow B\underset{\underset{O}{\|}}{C}OR + R\underset{\underset{CO_2R}{|}}{C}{=}NO_2^{\ominus}$$

I

This degradation of nitromalonates to nitroacetates by sodium hydride was employed to achieve a general synthesis of α-nitro esters. The procedure was based on nitration of substituted malonic and acetoacetic esters with acetone cyanohydrin nitrate in the presence of an excess of sodium hy-



$$\begin{matrix} RCH(CO_2C_2H_5)_2 \\ \text{or} \\ R\underset{\underset{COCH_3}{|}}{C}HCO_2C_2H_5 \end{matrix} + (CH_3)_2\underset{\underset{CN}{|}}{C}ONO_2 \xrightarrow{2NaH} R\underset{\underset{NO_2}{|}}{C}HCO_2C_2H_5$$

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[1] This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

[2] W. Wislicenus and A. Endres, *Ber.*, **35**, 1755 (1902).

[3] W. Wislicenus and H. Wren, *ibid.*, **38**, 502 (1905).

[4] W. Wislicenus and M. Waldmüller, *ibid.*, **41**, 3338 (1908).

[5] H. Wieland, P. Garbsch and J. J. Chavan, *Ann.*, **461**, 295 (1928).

[6] R. L. Shriner and E. A. Parker, THIS JOURNAL, **55**, 766 (1933), *et seq.*

[7] W. D. Emmons and J. P. Freeman, *ibid.*, **77**, 4387 (1955).

[8] A study of this reaction is underway and will be reported at a later date.

[9] C. Ulpiani, *Atti. accad. Lincei*, [5] **13**, II, 346 (1904); *Brit. Abstr.*, **88**, 9 (1905).

[10] W. Steinkopf and A. Supan, *Ber.*, **53**, 3248 (1910).

TABLE I

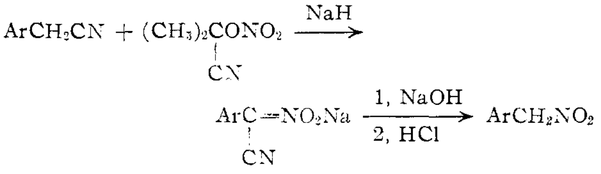
α-NITRO ESTERS ($R\overset{NO_2}{C}HCO_2C_2H_5$) FROM SUBSTITUTED MALONIC AND ACETOACETIC ESTERS

R	Yield, % from Malonic ester	Yield, % from Acetoacetic ester	B.p. °C.	B.p. Mm.	$n^{20}D$	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
H[a]	42	52	42–43	0.2	1.4260						
CH_3[b]	56	..	46	.5	1.4208	40.81	41.40	6.16	6.35	9.52	9.08
C_2H_5[b]	51	46	50–52	.5	1.4239	44.72	45.06	6.88	6.62	8.69	8.30
n-C_3H_7	48	46	51–52	.1	1.4274	47.99	48.88	7.48	6.99	8.00	8.68
n-C_4H_9	54	50	61–63	.5	1.4300	50.78	50.84	7.99	6.86	..	..
iso-C_4H_9	47	..	58–59	.5	1.4281	50.78	50.68	7.99	7.63	7.40	8.07
n-C_5H_{11}	46	70	62–64	.2	1.4354	53.18	54.01	8.44	9.16	6.89	6.83
iso-C_5H_{11}	..	69	73–75	.5	1.4349	53.18	53.82	8.44	8.50	6.89	7.47
$C_6H_5CH_2$	67	..	88–90	.02	1.5050	59.18	59.22	5.87	5.70	6.28	5.90
$ClCH_2CH_2CH_2$	40	..	88–90	.1	1.4565	40.12	40.28	5.77	5.33	6.68	6.26
$CH_2{=}CHCH_2$	45	53	46–48	.15	1.4407	48.55	48.11	6.40	6.09	8.09	8.32
C_6H_5[c]	57	..									

[a] Lit. values[11]: b.p. 105–107° (25 mm.); $n^{20}D$ 1.4252. [b] These compounds have been reported as unpurified oils.[10] [c] This compound has previously been prepared by nitration of ethyl phenylacetate.[2] In this investigation no effort was made to purify this material. Its structure was established by its method of preparation and the similarity of its infrared spectrum to those of the other α-nitro esters.

dride. Comparable yields were obtained from either starting material; the experimental results are summarized in Table I. This reaction constitutes the most general method for the preparation of α-nitro esters now available. While nitroacetic esters can be obtained by the alkaline condensation of nitromethane,[11] the higher homologs are poorly characterized and relatively inaccessible. Previous methods have involved direct nitration of substituted malonic esters followed by alkaline cleavage of an ester group (both poor reactions as previously reported),[9,10] or nitrosation of acetoacetic esters to α-oximino esters followed by oxidation.[12] The present method has the particular advantages of being a one-step procedure and can be used with molecules containing functional groups, *e.g.*, aromatic rings, that would be attacked by the usual nitrating mixtures.

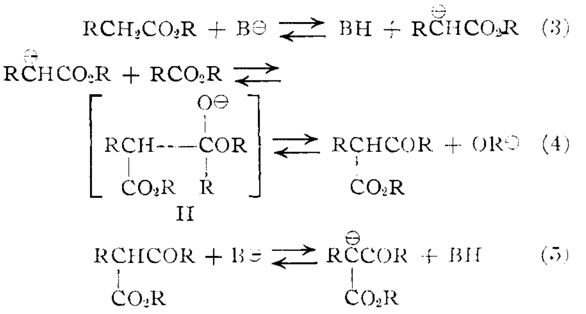
Arylacetonitriles are also attacked by acetone cyanohydrin nitrate to yield the corresponding nitroacetonitrile derivatives. These intermediates were not purified but were converted to the corresponding arylnitromethanes in the usual manner.[13]



$$ArCH_2CN + (CH_3)_2\underset{CN}{C}ONO_2 \xrightarrow{NaH} Ar\underset{CN}{C}{=}NO_2Na \xrightarrow[2,\ HCl]{1,\ NaOH} ArCH_2NO_2$$

In this way phenylacetonitrile was converted to phenylnitromethane in 70% over-all yield and *o*-chlorophenylnitromethane was obtained from *o*-chlorophenylacetonitrile in 42% yield. Efforts to nitrate less active methylene compounds such as *t*-butyl acetate, acetophenone and diethyl succinate were unsuccessful.

The Claisen condensation may be used as the point of departure for a discussion of the probable mechanism of the alkaline nitration reaction. This reaction may be represented by equations 3–5[14]



$$RCH_2CO_2R + B^{\ominus} \rightleftharpoons BH + R\overset{\ominus}{C}HCO_2R \quad (3)$$

$$R\overset{\ominus}{C}HCO_2R + RCO_2R \rightleftharpoons \underset{\text{II}}{\left[\underset{CO_2R}{RCH}\text{---}\underset{R}{\overset{O^{\ominus}}{C}}OR\right]} \rightleftharpoons \underset{CO_2R}{RCH}COR + OR^{\ominus} \quad (4)$$

$$\underset{CO_2R}{RCH}COR + B^{\ominus} \rightleftharpoons R\underset{CO_2R}{\overset{\ominus}{C}}COR + BH \quad (5)$$

The essential difference between the Claisen condensation and alkaline nitration of active methylene compounds lies in the difference between the carbonyl group and the nitro group. Addition to either of these groups requires that the oxygen atoms absorb the negative charge. A carbonyl oxygen atom accepts it readily and as a result the carbonyl group is attacked by anions of widely varying base strength. The nitro group is resistant to addition reactions since an intermediate of wide charge separation results. Thus it is reasonable to assume that the nitro group will react *additively* only with very reactive anions.

Alkaline nitration with a simple nitrate ester such as ethyl nitrate probably follows the course of the Claisen reaction very closely in all respects. The main limitation on the reaction is that it is useful only for very reactive anions. Thus anions derived from fluorene, arylacetonitriles and cyclic ketones react with ethyl nitrate. However, the cyclic ketone nitration with ethyl nitrate suffers greatly from a competitive self-condensation reaction. Furthermore, it has been shown in this investigation that ethyl nitrate is not attacked by sodio malonic ester, a relatively stable anion, even when the latter is preformed irreversibly in high concentration. The unique structural characteristics of acetone cyanohydrin nitrate set it apart

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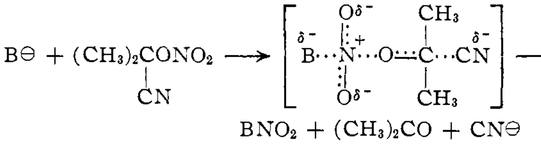
(11) H. Feuer, H. B. Hass and K. S. Warren, THIS JOURNAL, **71**, 3078 (1949).

(12) J. Schmidt and K. Widmann, *Ber.*, **42**, 1893 (1909).

(13) A. P. Black and F. H. Babers in A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 512.

(14) C. R. Hauser and B. E. Hudson, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 267.

from other nitrate esters and, correspondingly, probably modify the key step of the nitration reaction. It is suggested that when acetone cyanohydrin nitrate is employed, an intermediate of type II in equation 4 is not actually formed. Instead the reaction amounts to a displacement on nitrogen, *i.e.*, the negative charge is transferred in the transition state from the reacting anion to the nitrile group instead of to the oxygen atoms of the nitro group (equation 6). The driving force for this charge transfer is the concerted formation of the carbon–oxygen double bond. Such a picture explains the reactivity of acetone cyanohydrin nitrate



$$B^{\ominus} + (CH_3)_2C(CN)ONO_2 \longrightarrow \left[\overset{\delta-}{B}\cdots\overset{+}{N}(O^{\delta-})_2\cdots O\cdots C(CH_3)_2\cdots \overset{\delta-}{CN}\right] \longrightarrow BNO_2 + (CH_3)_2CO + CN^{\ominus} \quad (6)$$

toward anions that do not attack ordinary nitrate esters. This mechanism has also been used to explain the nitration of amines with this reagent.[7]

Experimental[15]

Diethyl Nitromalonate.—A solution of 48.0 g. (0.3 mole) of diethyl malonate in 150 ml. of dry tetrahydrofuran was added slowly to a slurry of 7.2 g. (0.3 mole) of sodium hydride in 200 ml. of tetrahydrofuran. This mixture was stirred under reflux for 30 minutes following the addition and then cooled to room temperature. A solution of 13.0 g. (0.1 mole) of acetone cyanohydrin nitrate[7] in 100 ml. of tetrahydrofuran was added and the mixture was stirred under reflux for two hours. Any unreacted hydride was decomposed by the addition of ethanol and the mixture was poured into 500 g. of ice containing 25 ml. of concentrated hydrochloric acid. This mixture was extracted with ether. The resulting organic extracts were extracted several times with 10% sodium hydroxide solution. These basic extracts were washed with ether and acidified with ice-cold 10% hydrochloric acid. The oil that separated was extracted with ether, dried and, after removal of the solvent, distilled to yield 9.2 g. (45%) of diethyl nitromalonate, b.p. 78–80° (0.2 mm.), $n^{20}\text{D}$ 1.4275 (lit. values[16] b.p. 81–83° (0.3 mm.), $n^{21}\text{D}$ 1.4274).

Preparation of α-Nitro Esters. General Method.—To a suspension of 5.0 g. (0.21 mole) of sodium hydride in 100 ml. of tetrahydrofuran was added 0.1 mole of the appropriate malonic or acetoacetic ester in 75 ml. of tetrahydrofuran. The mixture was heated under reflux for 30 minutes to ensure complete formation of the sodio derivative, and then cooled to room temperature. A solution of 19.5 g. (0.15 mole) of acetone cyanohydrin nitrate in 75 ml. of tetrahydrofuran was added slowly. After addition was complete, the mixture was heated under reflux for two hours and worked up as described for diethyl nitromalonate. All the α-nitro esters prepared had bands in their infrared spectra at 1748 and 1560 cm.$^{-1}$ attributable to carboxylic ester and nitro groups, respectively.

Phenylnitromethane.—The sodio derivative of phenylacetonitrile was prepared from 11.7 g. (0.1 mole) of the nitrile and 5.0 g. (0.21 mole) of sodium hydride in 200 ml. of tetrahydrofuran. This mixture was cooled to 15° and a solution of 19.5 g. (0.15 mole) of acetone cyanohydrin nitrate in 75 ml. of tetrahydrofuran was added at such a rate that the temperature of the reaction mixture did not rise above 30°. It was stirred at 30–35° for an hour and then stored in the refrigerator overnight. Dry ether was added and the precipitated solid was collected on a filter. This material, presumably a mixture of sodium phenylnitrocyanomethide and sodium cyanide, amounted to 22 g. (94%). The hydrolysis and acidification steps were carried out exactly as described by Black and Babers.[13] Phenylnitromethane was obtained as a pale yellow oil; yield 9.6 g. (70%).

o-Chlorophenylnitromethane.—By the same method as described for the preparation of phenylnitromethane, *o*-chlorophenylacetonitrile[17] (15.1 g., 0.1 mole) was converted to *o*-chlorophenylnitromethane, b.p. 74–76° (0.2 mm.), $n^{20}\text{D}$ 1.5532; yield 8.2 g. (42%).

Anal. Calcd. for $C_7H_6NO_2Cl$: C, 49.00; H, 3.53; N, 8.16; Cl, 20.69. Found: C, 49.09; H, 3.26; N, 9.15; Cl, 20.79.

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[15] We are indebted to Miss Annie Smelley for the microcombustion data and to Dr. Keith S. McCallum for infrared interpretations.

[16] D. I. Weisblat and D. A. Lyttle, THIS JOURNAL, **71**, 3079 (1949).

[17] H. Mehner, *J. prakt. Chem.*, [2] **62**, 554 (1900).

HUNTSVILLE, ALABAMA

[CONTRIBUTION FROM THE BAKER CHEMISTRY LABORATORY OF CORNELL UNIVERSITY AND FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF SOUTH CAROLINA]

Some Reactions of an Optically Active Diazonium Salt and of an Optically Active Diacyl Peroxide

BY DELOS F. DETAR[1] AND JOHN CHARLES HOWARD[2]

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The thermal decomposition of the optically active peroxide of 2-methyl-6-nitro-2′-biphenylcarboxylic acid (I) in benzene, in carbon tetrachloride, and in bromotrichloromethane leads to replacement of the carboxyl function by phenyl, by chlorine or by bromine. The products are optically active, but have undergone some racemization. Since the starting materials and products are thermally stable toward racemization under the reaction conditions, the partial racemization occurred during the reaction. This result is not possible if the products were formed only by the reaction RCOO· + SY → RY + S· + CO_2, and shows that the radical RCOO· must undergo decarboxylation prior to reaction with the solvent. A parallel study has been carried out on the diazonium salt derived from 2-methyl-6-nitro-2′-aminobiphenyl (II).

Optically active biphenyls have been used effectively in the study of reaction mechanisms, notably in studies of the Hofmann rearrangement,[3] of the Curtius rearrangement,[4] of the Wolff rearrangement,[5] and indirectly in determining the direction of migration in the Beckmann rearrangement.[6] A typical example is the conversion of the optically active azide derived from 2-methyl-6-nitro-2′-biphenylcarboxylic acid (I) to the optically active amine, 2-methyl-6-nitro-2′-aminobiphenyl

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[2] Rohm and Haas Research Assistant, 1951–1953, at Cornell University.

[3] E. S. Wallis and W. W. Moyer, THIS JOURNAL, **55**, 2598 (1933).

[4] F. Bell, *J. Chem. Soc.*, 835 (1934).

[5] J. F. Lane and E. S. Wallis, *J. Org. Chem.*, **6**, 443 (1941).

[6] J. Meisenheimer, W. Theilacker and O. Beisswenger, *Ann.*, **495**, 249 (1932).