[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

A New Synthesis of α-Nitroesters[1,2]

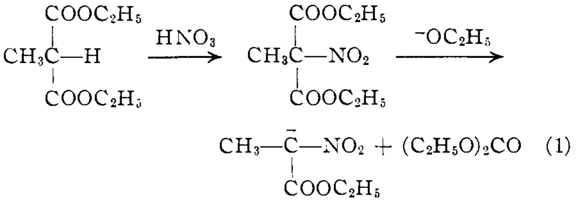
BY NATHAN KORNBLUM, ROBERT K. BLACKWOOD AND JACK W. POWERS

RECEIVED SEPTEMBER 17, 1956

A simple new synthesis of α-nitroesters which involves treating α-haloesters with sodium nitrite in the presence of phloroglucinol is described; 66 to 91% yields of pure α-nitroesters are obtained.

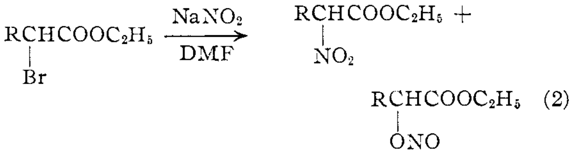
While α-nitroesters have been prepared on a number of occasions, none of the methods employed can be characterized as genuinely useful.[3] For example, while the reaction of α-iodoesters with silver nitrite gives 77–84% yields of α-nitroesters,[4] it suffers from important drawbacks. The readily available α-bromoesters react so slowly that they cannot be used and, so, must first be converted to α-iodoesters. Even with α-iodoesters the reaction is so slow, despite the use of a 100% excess of silver nitrite, as to be impractical for the preparation of any but low molecular weight, straight chain, α-nitroesters.[4]

Nitration of malonic esters and subsequent alkaline degradation as, for example, in eq. 1 has been used, but the isolation of pure products is difficult and the yields are low (15–22%).[5]



$$\mathrm{CH_3\overset{COOC_2H_5}{\underset{COOC_2H_5}{C}}{-}H} \xrightarrow{\mathrm{HNO_3}} \mathrm{CH_3\overset{COOC_2H_5}{\underset{COOC_2H_5}{C}}{-}NO_2} \xrightarrow{\mathrm{^-OC_2H_5}} \mathrm{CH_3{-}\overset{-}{\underset{COOC_2H_5}{C}}{-}NO_2} + \mathrm{(C_2H_5O)_2CO} \quad (1)$$

As pointed out previously[6] the reaction of organic halides with sodium nitrite requires a solvent which will dissolve both reactants; this immediately rules out most common solvents. Dimethylformamide (DMF) not only has the requisite solvent properties but, in addition, the reaction in this medium is very rapid so that processes which destroy the initially produced nitroparaffin and alkyl nitrite do not have a chance to intrude.[6,7] When, however, an attempt was made to carry out the reaction of equation 2, none of the α-nitroester could be isolated even though the α-bromoester was consumed rapidly; instead, by the joint action of the nitrite ester and sodium nitrite,[7] the initially produced α-nitroester was very quickly converted into the α-oximinoester.



$$\mathrm{R\underset{Br}{C}HCOOC_2H_5} \xrightarrow[\mathrm{DMF}]{\mathrm{NaNO_2}} \mathrm{R\underset{NO_2}{C}HCOOC_2H_5} + \mathrm{R\underset{ONO}{C}HCOOC_2H_5} \quad (2)$$

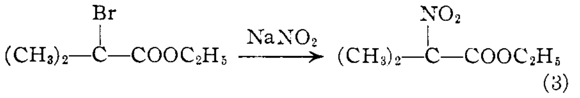
It transpires, however, that simply by adding phloroglucinol to the reaction mixture the formation of oximinoesters is prevented and pure α-nitroesters are obtained in excellent yields (Table I). The phloroglucinol functions as a scavenger for nitrite esters and is especially effective for this purpose. That this attribute of phloroglucinol is involved is shown by the production of ethyl α-nitroisobutyrate in 78–91% yields without phloroglucinol being present (eq. 3). Here the α-nitroester being devoid of α-hydrogen cannot undergo the nitrosation reaction which converts α-nitroesters to α-oximinoesters.[7]

TABLE I

SYNTHESIS OF α-NITROESTERS FROM α-BROMOESTERS

Ethyl α-nitroester	Reaction time,[c] hr. In DMSO	Reaction time,[c] hr. In DMF	Yield, % In DMSO	Yield, % In DMF
Propionate[a]	1.5	2	66	62
Butyrate	1.5	2.5	83	70–75
Valerate	1.5	...	87	..
Caproate	1	5	76	74
Isobutyrate[b]	5	44	91	78
Isovalerate	75	150	75	67
α-Phenyl-α-nitroacetate	..	2.5	..	70

[a] From ethyl α-chloropropionate a 68% yield of ethyl α-nitropropionate was obtained (solvent DMSO; reaction time 48 hr.). A run employing ethyl α-iodopropionate in DMF gave a 62% yield of ethyl α-nitropropionate after 2 hr. [b] No phloroglucinol employed. [c] DMF solutions *ca.* 0.5 molar in RBr and *ca.* 0.8 molar in $NaNO_2$. DMSO solutions *ca.* 1.2 molar in RBr and *ca.* 2 molar in $NaNO_2$.



$$\mathrm{(CH_3)_2{-}\overset{Br}{C}{-}COOC_2H_5} \xrightarrow{\mathrm{NaNO_2}} \mathrm{(CH_3)_2{-}\overset{NO_2}{C}{-}COOC_2H_5} \quad (3)$$

It also has been found that the reaction can be conducted in dimethyl sulfoxide (DMSO); in fact, DMSO is somewhat superior to DMF in the α-nitroester synthesis (*cf.* Table I). This superiority appears to derive principally from the distinctly greater solubility of sodium nitrite in DMSO; less solvent is needed and shorter reaction times are required.[8]

---

[1] Paper XVI in the Series "The Chemistry of Aliphatic and Alicyclic Nitro Compounds." A preliminary account of this work appeared in *Chemistry & Industry*, 443 (1955).

[2] This research was supported, in part, by grants from The Explosives Department of E. I. du Pont de Nemours and Co. and, in part, by the United States Air Force under Contract No. AF18(600)-310 monitored by the Office of Scientific Research, Air Research and Development Command.

[3] For a complete review see the Ph.D. thesis of J. H. Eicher, Purdue University, 1952.

[4] N. Kornblum, M. E. Chalmers and R. Daniels, THIS JOURNAL, **77**, 6654 (1955).

[5] C. Ulpiani, *Gazz. chim. ital.*, **35**, I, 273 (1905); W. Steinkopf and A. Supan, *Ber.*, **43**, 3246 (1910); A. K. MacBeth and D. Traill, *J. Chem. Soc.*, **127**, 892 (1925); N. Kornblum and J. H. Eicher, THIS JOURNAL, **78**, 1496 (1956). Subsequent to our preliminary communication,[1] W. D. Emmons and J. P. Freeman [THIS JOURNAL, **77**, 4391 (1955)] described a modification of the Ulpiani procedure which, while an improvement, remains much inferior to the synthesis of α-nitroesters from α-bromoesters and sodium nitrite.

[6] N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto and G. E. Graham, THIS JOURNAL, **78**, 1497 (1956).

[7] N. Kornblum, R. K. Blackwood and D. D. Mooberry, *ibid.*, **78**, 1501 (1956).

[8] A rough rate study made using ethyl α-bromobutyrate shows that the reaction with sodium nitrite occurs at essentially the same rate in DMSO and in DMF (25°); *cf.* Experimental.

Irrespective of whether DMSO or DMF is used, the reaction of α-haloesters with sodium nitrite is carried out at room temperature and, as the data of Table I show, it makes readily available a wide variety of α-nitroesters. Especially noteworthy is the preparation, in excellent yield, of ethyl α-nitroisobutyrate (eq. 3), since *t*-alkyl halides on treatment with sodium nitrite yield olefins rather than *t*-nitro compounds.[6,9] It is also of interest that ethyl α-chloropropionate, in DMSO, gives as good a yield (68%) of ethyl α-nitropropionate as is obtained from the α-bromoester.[10]

In only one instance does the new α-nitroester synthesis fail. If ethyl bromoacetate is treated with sodium nitrite in the usual way, a very rapid reaction ensues, but no ethyl nitroacetate can be isolated.[11]

α-Nitroesters possessing an α-hydrogen are relatively strong acids. They dissolve slowly in aqueous sodium bicarbonate, the rate of solution being a function of the molecular weight of the ester; in aqueous sodium carbonate they dissolve after a few minutes and, with 10% aqueous sodium hydroxide, they go into solution almost instantaneously. From the salts the α-nitroesters are readily regenerated (at least from sodium carbonate solution) by aqueous acetic acid and urea.[12]

Table II shows the apparent pK_A values of several α-nitroesters and nitroparaffins in 50% aqueous ethanol.[13]

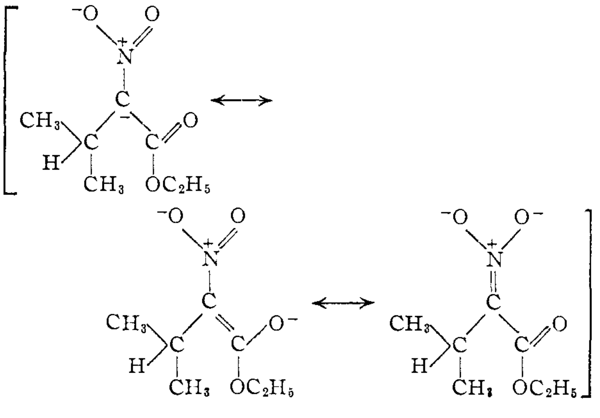
TABLE II

APPARENT pK_A VALUES IN 50% AQUEOUS ETHANOL

Compound	Apparent pK_A
Ethyl α-nitropropionate	7.5
Ethyl α-nitrobutyrate	7.6
Ethyl α-nitrocaproate	7.7
Ethyl α-nitroisovalerate	9.0
Ethyl α-nitro-α-phenylacetate	6.9
1-Nitrobutane	10
2-Nitrobutane	9.4
Phenylnitromethane	8.2
Benzoic acid	5.7[a]

[a] F. G. Bordwell and G. D. Cooper, THIS JOURNAL, **74**, 1058 (1952), report an apparent pK_A of 5.73.

Straight chain, secondary α-nitroesters are about 100 times stronger acids than 2-nitrobutane. It is also noteworthy that ethyl α-nitroisovalerate is distinctly less acidic than any of the other α-nitroesters. This may well be a case of steric inhibition of resonance.



Experimental

Reagents.[14]—N,N-Dimethylformamide (DMF, du Pont technical grade), phloroglucinol dihydrate (Ringwood technical grade) and dimethyl sulfoxide (DMSO, Stepan Chemical Co.) were used as received.[15] The α-bromoesters were commercial products which were rectified and only material of constant b.p. and $n^{20}D$ was used. Ethyl α-bromo-α-phenylacetate ($n^{20}D$ 1.5360) was specially prepared by Fairfield Laboratories. Sodium nitrite was an analytical grade.

The preparation of ethyl α-nitrobutyrate exemplifies the DMF procedure and that of ethyl α-nitrovalerate typifies the DMSO procedure. Reaction times are given in Table I.

Ethyl α-Nitrobutyrate.—Ethyl α-bromobutyrate (58.5 g., 0.30 mole) is poured into a stirred mixture of 600 ml. of DMF, 36 g. of sodium nitrite (0.52 mole) and 40 g. (0.32 mole) of anhydrous phloroglucinol (or 52 g. of phloroglucinol dihydrate; *cf.* footnote 15) in a 1-l. three-necked flask equipped with a sealed stirrer. The flask is stoppered, immersed in a water-bath maintained at room temperature, and stirring is continued for 2.5 hr. The reaction mixture is then poured into 1.2 l. of ice-water layered over with 300 ml. of diethyl ether. After separation of the upper layer, the aqueous phase is extracted four more times with 100-ml. portions of ether. The combined extracts are washed with four 100-ml. portions of water and then dried over anhydrous magnesium sulfate. The mixture is filtered with suction, the magnesium sulfate is washed with four 25-ml. portions of ether and these are combined with the filtrate. Using a small column, the ether is removed under reduced pressure, heat being supplied by a bath whose temperature is gradually raised to *ca.* 60°. The residual yellow liquid is transferred to a 100-ml. flask, the column is attached and the remaining solvent is removed under reduced pressure. Rectification of the residue yields 2–3 g. of forerun in the range 33–71° (1 mm.) which is followed by 34–36 g. (70–75%) of colorless ethyl α-nitrobutyrate (b.p. 71° (1 mm.), $n^{20}D$ 1.4233).

In the preparation of ethyl α-nitro-α-phenylacetate, the procedure was modified in that the crude product was not rectified; instead it was dissolved in aqueous sodium carbonate, regenerated with aqueous acetic acid and urea[12] and, finally, distilled.

The reaction is not critically dependent on conditions. Thus, using ethyl α-bromopropionate, the same yield of ethyl α-nitropropionate was obtained at 0° and at 25°.

---

(9) N. Kornblum and R. K. Blackwood, THIS JOURNAL, **78**, 4037 (1956).

(10) It is probable that α-chloroesters in DMF will also give excellent yields of α-nitroesters despite the somewhat longer reaction times which will be required.

(11) Precisely what happens has yet to be determined. Even lowering the reaction temp. to −20°, a device which is successful in the preparation of phenylnitromethane from benzyl bromide (ref. 6), fails to produce a trace of ethyl nitroacetate [W. M. Weaver, unpublished work].

(12) N. Kornblum and G. E. Graham, THIS JOURNAL, **73**, 4041 (1951).

(13) The apparent pK_A values in Table II are *ca.* 1.5 units higher than pK_A's determined in water. Thus, in water, benzoic acid has pK_A 4.20 [R. A. Benkeser and H. R. Krysiak, THIS JOURNAL, **75**, 2424 (1953)]; *cf.* also G. W. Wheland and J. Farr, *ibid.*, **65**, 1433 (1943).

(14) We thank the du Pont Co., the Ringwood Chemical Corporation and the Stepan Chemical Co. for generous gifts of DMF, phloroglucinol and DMSO, respectively.

(15) With ethyl α-nitrobutyrate, ethyl α-nitrovalerate and ethyl α-nitrocaproate, the yields were not altered (*cf.* Table I) by using phloroglucinol rendered anhydrous by heating for 3 hr. at 110° and DMSO which had been dried by standing over calcium hydride for several days. As regards reactions conducted in DMF, while all but one of the preparations summarized in Table I were carried out with anhydrous phloroglucinol, it is extremely probable that phloroglucinol dihydrate is equally effective. In experiments using ethyl α-bromopropionate and ethyl α-iodopropionate, phloroglucinol dihydrate gave 60–62% yields of ethyl α-nitropropionate, whereas with anhydrous phloroglucinol the yields were 62%.

Extension of the reaction time at 25° from 2 hr. to 17 hr. gave no loss in yield.

In reactions employing ethyl α-bromopropionate and ethyl α-iodopropionate, the use of half the amount of anhydrous phloroglucinol (20 g.) gave only 3 to 5% less ethyl α-nitropropionate. Other nitrate ester scavengers may be employed, but phloroglucinol seems to be far and away the most effective at destroying the nitrite ester formed along with the α-nitroester. Thus use of resorcinol (in the same molar concentration as an otherwise identical experiment using phloroglucinol) led to only a 25% yield of the α-nitropropionate along with an 8% yield of ethyl α-oximinopropionate. Furthermore, the rectified product, in spite of having correct refractive index, was highly colored.

In the conversion of ethyl α-bromoisobutyrate to the α-nitroester, the same yield (78%) was obtained in the presence and in the absence of phloroglucinol.

Ethyl α-Nitrovalerate.—Ethyl α-bromovalerate (60.9 g., 0.3 mole) is poured into a solution of 250 ml. of dimethyl sulfoxide (DMSO), 36 g. of sodium nitrite (0.52 mole) and 52 g. of phloroglucinol dihydrate (0.32 mole) in a 500-ml. three-necked flask equipped with a sealed stirrer. The flask is stoppered, immersed in a water-bath maintained at room temperature and stirring is continued for 1.5 hr. A slurry forms after *ca.* 0.5 hr., and, if necessary, a small amount of DMSO is added to facilitate stirring. The reaction mixture is then poured into 600 ml. of ice-water layered over with 200 ml. of diethyl ether. After separation of the upper layer, the aqueous phase is extracted four more times with 75-ml. portions of ether. The combined extracts are washed with four 100-ml. portions of water and then dried over anhydrous magnesium sulfate.

Using a small column the ether is removed at atmospheric pressure and the residual yellow liquid is rectified. This gives 44.2 g. (87% yield) of colorless ethyl α-nitrovalerate; b.p. 62° (1 mm.), n^{20}D 1.4266.

TABLE III

PHYSICAL CONSTANTS OF α-NITROESTERS

Ethyl α-nitroester	B.p. °C.	Mm.	n^{20}D	Literature[a] B.p. °C.	Mm.	n^{20}D
Propionate	55	1	1.4209	75	9	1.4210
Butyrate	71	1	1.4233	82	8	1.4233
Valerate[b]	62	1	1.4266			
Caproate	68	0.5	1.4300	80	3	1.4302
Isobutyrate[c]	46	1	1.4197			
Isovalerate[d]	60	1	1.4269			
α-Phenylacetate[e]	92	0.15	1.5098			

[a] Ref. 4. [b] *Anal.* Calcd. for $C_7H_{13}O_4N$: C, 47.99; H, 7.48. Found: C, 48.22; H, 7.69. [c] *Anal.* Calcd. for $C_6H_{11}NO_4$: C, 44.8; H, 6.89; N, 8.71. Found: C, 44.8, 44.6; H, 7.01, 7.11; N, 8.72. [d] *Anal.* Calcd. for $C_7H_{13}NO_4$: C, 48.0; H, 7.50; N, 8.00. Found: C, 47.9; H, 7.51; N, 8.03. [e] *Anal.* Calcd. for $C_{10}H_{11}NO_4$: C, 57.5; H, 5.30; N, 6.70. Found: C, 57.5; H, 5.48; N, 6.79.

Relative Reaction Rates in DMF and in DMSO.—In one arm of a two-armed flask was placed 50 ml. of 0.05 *N* ethyl α-bromobutyrate solution (0.488 g.) and in the other was placed 50 ml. of a solution which was 0.05 *N* in $NaNO_2$ (0.173 g.) and 0.05 *N* in anhydrous phloroglucinol. The flask was immersed in a constant temperature bath (25°), and after the two solutions had come to temperature they were mixed. Aliquots (5 ml.) were withdrawn, run into dilute sulfuric acid and titrated for bromide ion with 0.05 *N* $AgNO_3$. The following is a typical result and shows that the reaction of α-bromoesters with sodium nitrite occurs at essentially the same rate in DMF and in DMSO.

Time, min.	0.05 *N* $AgNO_3$ ml. DMSO	DMF
1	0.25	0.31
5	0.80	0.90
10	1.18	1.38
20	1.58	1.73
35	1.87	1.91
50	2.00	2.02
∞	2.50	2.50

The Reaction of Ethyl α-Bromopropionate with Sodium Nitrite in DMF without Phloroglucinol.—Ethyl α-bromopropionate (0.3 mole) was treated with sodium nitrite in DMF as described above except that no phloroglucinol was present. After 5.5 hr. the reaction mixture was worked up in the usual way. After removal of the ether 24.4 g. of a pale green, partly crystalline, residue remained. This, when treated with petroleum ether, gave 9.2 g. (24% yield) of ethyl α-oximinopropionate, m.p. 93.5–94°, mixed m.p. with authentic ethyl α-oximinopropionate, 94–94.5°. Concentration of the petroleum ether mother liquors left a green oil which, when rectified at 1 mm., gave no ethyl α-nitropropionate; it was not investigated further.

The Reaction of Ethyl α-Bromobutyrate with Sodium Nitrite in DMSO without Phloroglucinol.—Ethyl α-bromobutyrate (0.14 mole) was treated with sodium nitrite in DMSO as described above, except that no phloroglucinol was present. After 15 minutes the reaction mixture was worked up in the usual way. Distillation gave a 65% yield of ethyl α-oximinobutyrate, m.p. 59°, lit.[16] m.p. 58–60°.

***p*K$_A$ Determinations.**—The apparent *p*K$_A$ values given in Table II were determined at 25° by a procedure analogous to that of Bordwell and Cooper.[17] A Beckman *p*H meter equipped with calomel and glass (sodium) electrodes and calibrated with standard buffers at *p*H 9.16 and 7.00 was employed. Solutions of the various nitro compounds (*ca.* 0.01 *M*) in 50% (by volume) aqueous ethanol were titrated with aqueous sodium hydroxide (0.0967 *N*). An equal volume of absolute ethanol was added simultaneously from a second buret. The *p*H value at half-neutralization was taken as the *p*K$_A$ value. With the weaker acids several minutes were required before a constant, equilibrium reading could be obtained. In no case was more than 5 min. required and, in general, the time interval was inversely proportional to the acid strength. Since no special potassium glass electrode was employed, apparent *p*K$_A$ values above 9 must necessarily be only approximate, due to the electrode error above *p*H 9.

LAFAYETTE, INDIANA

---

[16] N. Kornblum and J. H. Eicher, THIS JOURNAL, **78**, 1494 (1956).

[17] F. G. Bordwell and G. D. Cooper, *ibid.*, **74**, 1058 (1952).