Nitration of Acetoacetate Esters by Acetyl Nitrate. A High Yield Synthesis of Nitroacetoacetate and Nitroacetate Esters[1]

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Received June 17, 1975

Reaction of acetoacetic esters (3) with acetyl nitrate (1) at −10 to 15° in the presence of catalytic amounts of strong protic acids or Lewis acids afforded 90–97% yields of the corresponding nitroacetoacetic esters (6). Under similar conditions, ethyl 3-acetoxy-2-butenoate (**10b**) produced 63% **6b** and 35% 3,4-bis(ethoxycarbonyl)furazan 2-oxide (**9b**) at 15°. In the absence of catalyst, reaction of ethyl acetoacetate (**3b**) was slow at 25° and the yields of **6b** and **9b** were 39 and 52%, respectively. A slow transformation of **6b** to **9b** took place at 22° in the presence of catalytic amounts of H_2SO_4 and the reaction was accelerated by acetic anhydride. Proton exchange evidence indicated that the crucial function of the acid catalyst in the nitration is to protonate **1** to provide an active nitrating species **2**, rather than merely accelerate enolization of **3**. In the presence of water, alcohols, or ammonia **6** cleaved quantitatively to nitroacetate esters and correspondingly acetic acid, acetate ester, or acetamide. The cleavage with water and alcohols was acid catalyzed. The combination of nitration and cleavage reactions affords a practical synthesis of nitroacetate esters.

Reaction of acetoacetate esters with absolute nitric acid in acetic anhydride at about 32° affords moderate (40–50%) yields of nitroacetate esters, the balance consisting mainly of the corresponding 3,4-bis(ethoxycarbonyl)furazan 2-oxides.[2] Nitric acid in acetic anhydride exists largely as acetyl nitrate.[3] In view of the mode of reaction of this reagent with enol esters,[4] it appeared reasonable that nitroacetoacetate esters are formed at least as intermediate species during the reaction with acetoacetate esters. Recently methyl nitroacetoacetate was synthesized by Babievskii et al.[5] by means of condensation reactions of methyl nitroacetate. The authors advanced the hypothesis that failure to prepare nitroacetoacetates by nitration of acetoacetates is due to the hydrolytic instability of the former, by analogy with the known hydrolytic instability of formylnitroacetic ester.[6]

Results and Discussion

Reaction of ethyl acetoacetate (**3b**, Scheme I) with a solution of 99% nitric acid (1 mol) in 2 mol of acetic anhydride (essentially acetyl nitrate in acetic acid) failed to proceed appreciably at 0° and was slow at ambient temperature. Two main products were detected by GLC, identified as ethyl nitroacetoacetate (**6b**) and 3,4-bis(ethoxycarbonyl)furazan 2-oxide (**9b**). In the presence of catalytic amounts of strong inorganic acids, such as sulfuric or perchloric, or Lewis acids, such as boron trifluoride etherate, reaction was fast even at −10° and **6b** was formed in essentially quantitative yield (reaction 1).

$$CH_3COCH_2CO_2R + AcONO_2 \rightarrow CH_3COCHNO_2CO_2R + AcOH \quad (1)$$

p-Toluenesulfonic acid was a less efficient catalyst and **9b** was produced in significant amounts along with **6b** (Table I). The reaction was also carried out using 70% nitric acid, in which case a larger amount of acetic anhydride was used in order to react with the water present in the 70% acid. The product was isolated from the reaction mixture by neutralizing the acid catalyst with anhydrous sodium carbonate and distilling under reduced pressure. If neutralization of the catalyst was omitted, extensive decomposition of **6b** to **9b** with simultaneous formation of acetic acid occurred on heating (vide infra). In similar manner the methyl, isopropyl, and cyclohexyl esters of acetoacetic acid were nitrated to the corresponding nitroacetoacetate esters. The NMR spectra of **6** in chloroform solution indicated the presence of 21–32% enol (**7**) in equilibrium with the keto form (Table II).

The behavior of the enol acetate of ethyl acetoacetate (**10b**, ethyl 3-acetoxy-2-butenoate, a mixture of cis and trans isomers) under the nitration conditions is of interest. In the presence of catalytic amounts of sulfuric acid, reaction was very slow at 0°. At 15° reaction was complete in about 50 min. The products formed were **6b** and **9b** in 63 and 35% yield, respectively. Under the same conditions **3b** gave essentially only **6b** (run 5 in Table I). When the reaction mixture from the nitration of either **3b** or **10b**, containing 1 mol % of sulfuric acid, was allowed to stand with-

Table I
Nitration of $CH_3COCH_2CO_2R$ (3) by $AcONO_2$[a]

Run	R (formula)	Nitration reagent	Catalyst (mol %)	Temp,[b] °C	Time,[b] min	Yield, %[c] 6	Yield, %[c] 9
1	Me (a)	*d*	$HClO_4$ (0.25)	−10	60	97	*e*
2	Et (b)	*f*	$HClO_4$ (0.20)	−10	60	97	2
3	Et (b)	*d*	BF_3 (1.0)	−10	45	98	1
4	Et (b)	*d*	H_2SO_4 (1.0)	−10	60	97	2
5	Et (b)	*d*	H_2SO_4 (1.0)	15	20	96	3
6	Et (b)	*f*	*p*-TSA[g] (2.5)	−5	65	91	7
7	Et (b)	*f*	None	25	60	39	52
8	*i*-Pr (c)	*d*	$HClO_4$ (0.25)	−10	60	93	*e*
9	Cyclohexyl (d)	*d*	$HClO_4$ (0.25)	−10	60	90	*e*

[a] All quantities of chemicals are referred to 3. [b] Temperature at which the last reagent (3 or the catalyst) was added to the nitration mixture, which was then maintained at that temperature for the stated time. [c] Yields determined by GLC. The yield of 6 was very close to the yield of $CH_2NO_2CO_2R$ obtained in a subsequent cleavage with an alcohol or water and isolated by distillation. [d] Ac_2O (6.0 mol) and 70.4% HNO_3 (1.02 mol). [e] Not determined. [f] Ac_2O (2.10 mol) and 99% HNO_3 (1.05 mol). [g] *p*-Toluenesulfonic acid.

Table II
Properties of Nitroacetoacetate Esters $CH_3COCHNO_2CO_2R$ (6) ⇄ $CH_3C(OH)=CNO_2CO_2R$ (7)

R (formula)	Bp, °C (mm)	Ir (neat), cm^{-1}	NMR ($CDCl_3$), δ[a] (multiplicity,[b] number of protons) CH_3CO	$CH_3C=$	$CHNO_2$	R	Enol (7), %[c]
Me (a)	75 (0.5)	1755, 1560	2.36 (s, 2.29)	2.23 (s, 0.71)	6.05 (s, 0.68)	3.81 (s, 3)	27 (32)
Et (b)	75 (0.2)	1750, 1567	2.40 (s, 2.24)	2.26 (s, 0.76)	6.13 (s, 0.69)	1.31 (t, 3) 4.35 (q, 2)	25 (30)
i-Pr (c)	66 (0.1)	1743, 1568	2.39 (s, 2.38)	2.25 (s, 0.62)	6.09 (s, 0.73)	1.32 (d, 6) 5.15 (m, 1)	21 (27)
Cyclohexyl (d)	70 (0.15)	1740, 1560	2.36 (s, 2.13)	2.22 (s, 0.87)	6.07 (s, 0.68)	~1.5 (b, 10) 4.9 (b, 1)	29 (32)

[a] Relative to tetramethylsilane. [b] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. [c] Calculated from $CH_3C=$ protons; number in parentheses calculated from $CHNO_2$ protons.

out prior neutralization of the acid catalyst, **6b** was slowly transformed to **9b**. The reaction followed first-order kinetics with respect to **6b** with a half-life of 22 hr at 22°. No such transformation took place if the acid catalyst was neutralized by addition of anhydrous sodium carbonate. Pure **6b** in acetic acid solution was indefinitely stable at room temperature but decomposed to **9b** at a similar rate in the presence of 10 mol % of sulfuric acid. The rate increased by one order of magnitude when the solvent was a 1:1 (v/v) mixture of acetic acid and acetic anhydride (Table III).

The following reaction mechanism is consistent with the experimental results of the nitration of **3b** and **10b** and the transformation of **6b** to **9b** (Scheme I). The active nitrating species in a mixture of acetic anhydride and nitric acid is the protonated acetyl nitrate (**2**).[3] The concentration of **2** is greatly increased in the presence of a strong protic acid. A Lewis acid apparently creates an equally strong electrophile by withdrawing electrons from **1**; e.g., in the case of boron trifluoride the species $AcONO_2BF_3$ is assumed. Obviously the role of acid in the nitration also involves catalysis of the enolization of **1** (reaction 2). Proton NMR spectra of a 20 vol % solution of ethyl acetoacetate in acetic acid-d_4 revealed exchange of the active methylene protons at 0° with a half-life equal to 52 min. Addition of 2 mol % of sulfuric acid accelerated the rate of exchange by a factor of about 5 (half-life 10 min). In both cases the ester existed in the enol form, **4b**, to the extent of about 20%. As stated earlier, no appreciable nitration of ethyl acetoacetate took place at 0° in the absence of acid catalyst upon treatment with **1** in acetic acid. It is evident that **1** does not react with **4** unless it is first activated via protonation to **2**. The proton exchange data show that the acid catalyst also accelerates the rate of enolization of **3**. It is clear from the experimental data, however, that the crucial function of the acid is in assisting the formation of the nitrating species **2**. This species adds to **4** with formation of acetic acid to yield the α-nitrohydroxycarbonium ion, **5** (reaction 3). Ejection of a proton from **5** affords nitroacetoacetate ester **6** and/or its enol form **7** (reaction 4). The formation of **9** can be explained by cleavage of **5** to a nitrile oxide **8**, which then dimerizes (reactions 5 and 6). The high yields of **6** obtained during the acid-catalyzed nitration of **3** indicate that reaction 4 is much faster than reaction 5. The first-order transformation of **6b** to **9b** in the presence of acid catalyst is reasonably explained by reversal of reaction 4, followed by reactions 5 and 6.

The increased yields of **9b** obtained during nitration of **10b** can be explained in the following manner. The carbonium ion, **11b**, formed in this case cannot, unlike **5b**, be transformed to **6b** by simple ejection of a proton but must rather eject an acylium ion (reaction 8). Cleavage to acetic anhydride and **8b** (reaction 9) is apparently a competitive alternative. The acceleration of the acid-catalyzed transformation of **6b** to **9b** in the presence of acetic anhydride presumably involves formation of **11b** via **5b** and/or **7b** fol-

Table III
Conversion of Ethyl Nitroacetoacetate (6b) to Diethyl 2-Oxofurazandicarboxylate (9b)[a]

Run	Reaction medium	Additive (mol %)[b]	Half-life, hr
10	AcOH	H_2SO_4 (10)	24
11	AcOH–Ac_2O equal volumes	H_2SO_4 (10)	2.1
12	Aliquot from run 4[c,d]	None[d]	22
13	Aliquot from run 4[c,e]	None[e]	No reaction

[a] Reaction at 22°, concentration of **6b** was 0.25 *M*, unless otherwise mentioned. [b] Referred to **6b**. [c] Concentration of **6b** was ~1.3 *M*; Ac_2O–AcOH ~ 350:400 (molar ratio). [d] Aliquot taken before addition of Na_2CO_3. [e] Aliquot taken after addition of Na_2CO_3.

Scheme I

$$Ac_2O + HNO_3 \underset{AcOH}{\overset{-AcOH}{\rightleftharpoons}} AcONO_2 \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} (AcOHNO_2)^+$$
(1) (2)

$$CH_3COCH_2CO_2R \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} CH_3\overset{+}{C}(OH)CH_2CO_2R \underset{H^+}{\overset{-H^+}{\rightleftharpoons}} CH_3C(OH)=CHCO_2R \quad (2)$$
(3) (4)

$$2 + 4 \longrightarrow CH_3\overset{+}{C}(OH)CHNO_2CO_2R + AcOH \quad (3)$$
(5)

$$5 \underset{H^+}{\overset{-H^+}{\rightleftharpoons}} CH_3COCHNO_2CO_2R \text{ or } CH_3C(OH)=CNO_2CO_2R \quad (4)$$
(6) (7)

$$5 \longrightarrow O\leftarrow N\equiv CCO_2R + AcOH + H^+ \quad (5)$$
(8)

$$2\,8 \longrightarrow \quad (6)$$
(9)

$$2 + CH_3C(OAc)=CHCO_2R \longrightarrow$$
(10)

$$CH_3\overset{+}{C}(OAc)CHNO_2CO_2R + AcOH \quad (7)$$
(11)

$$11 \underset{Ac^+}{\overset{-Ac^+}{\rightleftharpoons}} 6 \text{ or } 7 \quad (8)$$

$$11 \longrightarrow 8 + Ac_2O + H^+ \quad (9)$$

R = Me (a), Et (b), *i*-Pr (c), cyclohexyl (d)

Table IV
Cleavage of Ethyl Nitroacetoacetate (6b)[a]

Run	Nucleophile[b]	Additive (mol %)[c]	Half-life, min	Product[d]
14	MeOH	None	66	AcOMe
15	MeOH	NaOMe (10)	2.3×10^2	AcOMe
16	EtOH	None	5.8×10^2	AcOEt
17	EtOH	Et_3N (140)	$>10^4$	AcOEt
18	EtOH	$HClO_4$ (10)	<1	AcOEt
19	EtOH	$HClO_4$ (1)	5.5	AcOEt
20	H_2O[e]	None	40	AcOH
21	NH_3[f]	None	<1	$AcNH_2$

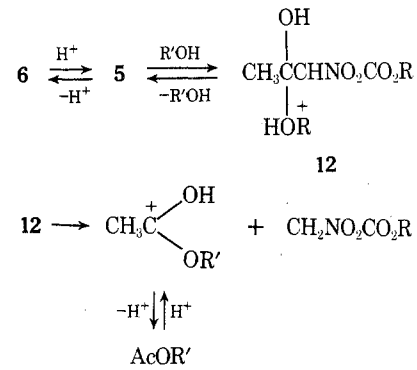
[a] Reaction at 22°, concentration of 6b was 0.5 *M*. [b] Neat, unless otherwise mentioned. [c] Referred to 6b. [d] Besides ethyl nitroacetate. [e] Mixed with two volumes of acetone. [f] As 14 *M* aqueous solution.

lowed by reactions 9 and 6. Formation of oxofurazans during nitration of enol esters of simple ketones has not been observed.[4] It is likely that the role of the ethoxycarbonyl group of **11b** is to stabilize the nitrile oxide (8) by delocalizing the C≡N triple bond. Transient formation of nitrile oxides has been postulated in the decomposition of α-nitro ketones with excess strong mineral acid.[7] In that medium the nitrile oxides hydrolyze to carboxylic acids and hydroxylamine salts, which are the products isolated from the reaction mixture.

The nitroacetoacetate esters cleaved quantitatively to nitroacetate esters upon reaction with water, alcohols, or ammonia. The cleavage by water and alcohols was catalyzed by acids and followed first-order kinetics with respect to the substrate. The rate of cleavage decreased in the order water > methanol > ethanol (Table IV). The mechanism that best fits these data is fast protonation of **6** to **5** followed by nucleophilic attack of alcohol or water on **5** and cleavage of the hemiketal, **12**, formed (Scheme II). Hemiketals have been postulated as intermediates in the acid-catalyzed cleavage of α-nitro ketones in alcohol solution.[8] In the presence of base the cleavage of **6b** by alcohols was inhibited. Since base-catalyzed cleavage of α-nitro ketones is known,[9] an explanation is in order. The most likely reason for the inhibition is the fact that **6b** is a relatively strong acid with pK_a estimated to be about 2.4. Owing to the acidity of **6b**, less than stoichiometric amounts of added base are completely neutralized. The acidity of the reaction medium is reduced in the process, and as a result the acid-catalyzed cleavage is hindered without compensation by a base-catalyzed reaction. In the presence of excess base **6b** is completely ionized and therefore less amenable to attack by RO^- or OH^-. Aqueous ammonia, however, cleaved **6b** to ethyl nitroacetate and acetamide in a few minutes at room temperature.

For preparative purposes it is not necessary to isolate **6** in order to obtain nitroacetate esters. Ethyl nitroacetate was very conveniently prepared in over 90% yield by nitrating ethyl acetoacetate in the presence of an acid catalyst and cleaving the nitroacetoacetate formed without isolation by adding ethanol to the reaction mixture after all the acetoacetate had reacted. The catalyst was then neutralized by addition of sodium carbonate and the mixture was fractionally distilled under reduced pressure. Failure to neutralize the catalyst resulted in partial decomposition of ethyl nitroacetate during distillation accompanied by formation of **9b**. The distilled nitroacetate had a faintly yellow color but otherwise was indistinguishable from authentic material. Colorless material could be obtained in an alternate work-up, in which the nitration mixture was treated with water and then extracted with dichloromethane. Ethyl nitroacetate was recovered by fractional distillation of the extract. This work-up is very similar to the practice of early

Scheme II



R = Me (**a**), Et (**b**), *i*-Pr (**c**), cyclohexyl (**d**)
R' = H, Me, Et

workers[2] and explains why **6b** had not been observed in the past in the nitration products of ethyl acetoacetate.

In conclusion it should be noted that the combination of nitration and cleavage reactions reported here constitutes a practical, high-yield synthesis of nitroacetate esters from acetoacetate esters.

Experimental Section

GLC analyses were carried out on a Packard gas chromatograph using 6-ft, 3-mm i.d. Pyrex columns of 10% SE-30 on acid-washed Chromosorb W or 10% Carbowax 20M on Teflon 6. Proton NMR spectra were recorded on either Varian A-60 MHz or HA-100 MHz instruments. All preparative reactions were routinely carried out under a nitrogen atmosphere.

Methyl acetoacetate (**3a**) and ethyl acetoacetate (**3b**) were purchased from Eastman. Other acetoacetates were prepared from **3a** by base-catalyzed transesterification with the appropriate alcohol; isopropyl acetoacetate (**3c**), bp 55° (4.5 mm); cyclohexyl acetoacetate (**3d**), bp 92–95° (2 mm). Both esters were characterized by NMR spectra. Nitric acid, 70.4%, was Baker and Adamson reagent grade. Nitric acid, 99%, was obtained from Essex Chemical, Clifton, N.J. It was distilled prior to use to afford a colorless fraction.

Proton Exchange of Ethyl Acetoacetate (3b) in Acetic Acid-d_4. Acetic acid-d_4 (0.40 ml) was mixed at 0° with **3b** (0.10 ml) and the NMR spectrum at 100 MHz was recorded at the same temperature immediately and every 15 min thereafter for 1 hr. The intensity of the peaks for $-COCH_2CO-$ (3.47 ppm, s) and C=CH– (4.95 ppm, s) diminished with first-order kinetics owing to proton–deuteron exchange. The half-life of the exchange was 52 min. The mole ratio of the enol to keto form, taken as equal to 2 H (4.95)/[2 H (4.95) + H (3.47)], remained essentially constant at 0.22 ± 0.02 during the experiment. When 0.8 μl of D_2SO_4 was added, the half-life of the exchange was reduced to 10 min.

Ethyl 3-Acetoxy-2-butenoate (10b). This was prepared by acetylation of **3b** with acetyl chloride in pyridine.[10] Analysis by GLC and NMR showed that the product consisted of a mixture of two cis–trans isomers in the ratio 30:70. The major component was the isomer with the methyl group cis to the ethoxycarbonyl group: bp 95–97° (10 mm); NMR ($CDCl_3$) δ 1.26 (t) and 1.28 (t, total 3 H), 2.02 (d, J = 1.10 Hz, 1 H) and 2.36 (d, J = 0.92 Hz, 2 H), 2.19 (s, 2.2 H) and 2.24 (s, 0.8 H), 4.13 (q) and 4.18 (q, total 2 H), 5.60 (q, J = 1.10 Hz, 0.35 H) and 5.67 (q, J = 0.92 Hz, 0.65 H). The doublets at δ 2.36 and 2.02 were assigned correspondingly to the methyl groups cis and trans to the ethoxycarbonyl function in accordance with numerous literature examples[11] showing that in similar systems the allylic methyl group of the cis isomer appears at lower field than the corresponding group of the trans isomer.[12] The assignment is consistent with the fact that the vinyl proton cis to the acetoxy function appears at a lower field (δ 5.67) than the corresponding trans proton (δ 5.60).[14]

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 56.25; H, 6.96.

Ethyl Nitroacetoacetate (6b). Concentrated H_2SO_4 (0.055 ml, 0.001 mol) was added to 57 ml (0.60 mol) of Ac_2O. The mixture was cooled to 10°, then 6.30 ml (0.102 mol) of 70.4% HNO_3 was added dropwise while the solution was well stirred and the temperature maintained at 10–15° with external cooling. The reaction mixture was cooled to −10° and 13.0 g (0.100 mol) of ethyl acetoacetate

Table V
Spectral Properties of Nitroacetate Esters

R	Ir (neat), cm^{-1}	NMR ($CDCl_3$), δ[a] (multiplicity,[b] number of protons) CH_2NO_2	R		Registry no.
Et	1760, 1567	5.20 (s, 2)	1.28 (t, 3)	4.25 (q, 2)	626-35-7
i-Pr	1750, 1560	5.16 (s, 2)[c]	1.30 (d, 6)	5.1 (m, 1)[c]	31333-37-6
Cyclohexyl	1740, 1560	5.12 (s, 2)	~1.5 (b, 10)	4.9 (b, 1)	75-36-5

[a] Relative to tetramethylsilane. [b] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. [c] Imperfectly resolved.

(**3b**) was added within 5 min. Temperature was maintained at −10° during addition and subsequently for 1 hr. Then the reaction mixture was allowed to warm to 21° and 0.31 g (0.003 mol) of anhydrous Na_2CO_3 was added. The color changed from pale yellow to yellow-orange. Analysis by GLC indicated that **3b** had reacted completely and that **6b** had been produced in 97% yield and **9b** in 2% yield. The bulk of volatiles was eliminated below 50° in the rotary evaporator. The residue was filtered and distilled under vacuum[15] to give 9.5 g (54%) of yellow liquid **6b**. Physical properties are shown in Table II.

Anal. Calcd for $C_6H_9NO_5$: C, 41.15; H, 5.18; N, 8.00. Found: C, 41.37; H, 5.25; N, 7.66.

Sodium Salt of Ethyl Nitroacetoacetate. A solution of 1.75 g (0.010 mol) of **6b** in 10 ml of MeOH was made and immediately treated at room temperature with a solution of 0.70 g (0.013 mol) of MeONa in 3 ml of MeOH. A white, crystalline precipitate formed. EtOH (30 ml) was added and the reaction mixture was stirred for 10 min and filtered. The product was washed with EtOH and dried in vacuo at 70°, yield 1.46 g (74%), mp 222–224° dec.

Anal. Calcd for $C_6H_8NO_5Na$: C, 36.54; H, 4.09; N, 7.11. Found: C, 36.32; H, 4.37; N, 6.83.

Estimate of the pK_a of Ethyl Nitroacetoacetate (6b). The sodium salt of **6b** (0.197 g, 1.00 mmol) was dissolved in 30 ml of 0.0167 *N* HCl (0.50 mequiv). The pH of the solution was monitored for 10 min at 22° with a combination glass–calomel electrode. The pH drifted from 2.71 to 4.04 during this time. A plot vs. time extrapolated at the origin to pH 2.4, which was taken as equal to the pK_a of **6b**. A second plot was obtained by mixing equimolar quantities of **6b** and its sodium salt dissolved respectively in MeOH and water. The total initial concentration of **6b** and its anion in the mixture was 0.035 *M* and the ratio of MeOH to water was 1:5 by volume. The two plots differed by less than 0.2 pH units at any time point and extrapolated to essentially the same value at the origin.

Ethyl Nitroacetate. A. With 70.4% Nitric Acid. The nitration procedure described in the synthesis of **6b** was repeated on a tenfold scale. *Caution: When working on this scale it is important to control the temperature as closely as possible. Best control was obtained by maintaining a Dry Ice–acetone bath on a jack below the reactor and lifting it as required.* Addition of **3b** was complete in 10 min. At the end of the nitration the temperature was raised to 21° and 500 ml of EtOH was added. The reaction mixture was allowed to remain for 1 hr at 30°, then 2.1 g (0.02 mol) of Na_2CO_3 was added and the mixture was concentrated in the rotary evaporator. The residue was filtered and the filtrate was fractionated under vacuum to yield 125 g (94%) of faintly yellow liquid ethyl nitroacetate: bp 70° (1.5 mm); ir (neat, NaCl plates) 1760, 1567 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (t, 3 H), 4.25 (q, 2 H), 5.20 (s, 2 H). Both spectra were similar to the spectra of a sample of ethyl nitroacetate prepared according to a literature method.[16] Identity was further confirmed by coinjection in two GLC columns with the same sample of ethyl nitroacetate.

B. With 99% Nitric Acid. To 200 ml (2.10 mol) of Ac_2O were added dropwise with good stirring 44 ml (1.05 mol) of colorless distilled 99% nitric acid. The temperature during addition was maintained at 0–5° by external cooling. The mixture was kept at 5° for an additional period of 5 min; then it was cooled to −15° and 130 g (1.00 mol) of **3b** was added at this temperature. No reaction was evident. To the reaction mixture was added dropwise a solution of 0.20 ml (0.002 mol) of 70% $HClO_4$ in 5 ml of acetic acid. Vigorous evolution of heat was evident during addition of catalyst but the temperature was maintained at −10°. Addition was complete in about 10 min. *Caution: It is important to maintain good temperature control. This was best accomplished by maintaining a Dry Ice–acetone bath on a jack under the reaction vessel and lifting it as required. In large-scale reactions with 99% HNO_3 the reaction was best controlled by adding the catalyst last.* After 1 more hr at −10°, the reaction mixture was allowed to reach 21° and was worked up as described under part A. Similar yields of ethyl nitroacetate were obtained and the product was faintly yellow. In an alternate work-up, the nitration mixture was stirred for 2 hr with 500 ml of water at room temperature, the mixture was extracted with methylene dichloride, and the extract was fractionated. The distilled product was colorless in this case, but the yield was the same.

Other Nitroacetoacetate Esters. Methyl nitroacetoacetate (**6a**), isopropyl nitroacetoacetate (**6c**), and cyclohexyl nitroacetoacetate (**6d**) were prepared in a similar manner as **6b** (Table I) and were characterized by ir and NMR spectra (Table II).

Other Nitroacetate Esters. Methyl nitroacetate, isopropyl nitroacetate, and cyclohexyl nitroacetate were obtained by cleavage of the corresponding crude nitroacetoacetates. The yields, based on the nitroacetoacetates charged, were essentially quantitative (GLC). The nitroacetates (except methyl nitroacetate) were characterized by ir and NMR spectra (Table V). The identity of methyl nitroacetate was confirmed by coinjection in two GLC columns with material prepared by a literature method.[16]

3,4-Bis(ethoxycarbonyl)furazan 2-Oxide (9b). This was isolated from the residue remaining after distillation of **6b**: yellow liquid, bp 98° (0.35 mm); NMR ($CDCl_3$) δ 1.39 (t) and 1.44 (t, total 6 H), 4.45 (q) and 4.50 (q, total 4 H).

Anal. Calcd for $C_8H_{10}N_2O_6$: C, 41.74; H, 4.38; N, 12.17. Found: C, 41.71; H, 4.50; N, 12.38.

Nitration of Ethyl 3-Acetoxy-2-butenoate (10b). Concentrated H_2SO_4 (0.011 ml, 0.0002 mol) was added to 11.4 ml of Ac_2O. The mixture was cooled to 10°, then 1.30 ml (0.021 mol) of 70.4% HNO_3 was added dropwise with good stirring while maintaining the temperature at 10–15° with external cooling, followed by 3.44 g (0.020 mol) of **10b**. After 50 min at 15°, Na_2CO_3 (0.10 g, 0.001 mol) was added and the mixture analyzed by GLC. It contained **6b** (63%) and **9b** (35%). The identities of both **6b** and **9b**, were confirmed by coinjection with the authentic compounds in two GLC columns.

Conversion of Ethyl Nitroacetoacetate (6b) to 3,4-Bis(ethoxycarbonyl)furazan 2-Oxide (9b). The conversion of **6b** to **9b** was carried out in vials immersed in a water bath maintained at 22°. The progress of the reaction was monitored by GLC. The concentration of **9b** was plotted vs. time as for a first-order reaction. The fit was reasonably good. The results are summarized in Table III.

Cleavage of Ethyl Nitroacetoacetate (6b). The cleavage of **6b** by various nucleophiles was carried out in vials immersed in a water bath maintained at 22°. The progress of the reaction was monitored by GLC. The concentration of **6b** was plotted vs. time as for a first-order reaction. The fit was reasonably good. First-order kinetics were assumed whenever the reaction was too fast to permit multiple analysis. The results are summarized in Table IV.

Acknowledgments. The author wishes to thank Mr. George E. Babbit for the NMR experiments.

Registry No.—**3a,** 105-45-3; **3b,** 141-97-9; **3c,** 542-08-5; **3d,** 6947-02-0; **6a,** 29291-62-1; **6b,** 51026-98-3; **6b** Na salt, 56689-02-2; **6c,** 51026-99-4; **6d,** 51027-00-0; **7a,** 30414-52-19; **7b,** 56689-03-3; **7c,** 56689-04-4; **7d,** 56689-05-5; **9b,** 18417-40-8; *trans*-**10b,** 27750-19-2; *cis*-**10b,** 26805-39-0; acetyl chloride, 75-36-5.

References and Notes

(1) Described in part in S. Sifniades, U.S. Patent 3,761,510 (1973), assigned to Allied Chemical Corp.
(2) (a) L. Bouveault and A. Wahl, *Bull. Soc. Chim. Fr.*, **31**, 847 (1904); (b) F. Arndt and T. D. Rose, *J. Chem. Soc.*, 1 (1935).
(3) F. G. Bordwell and E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **82**, 3588 (1960), and references cited therein.
(4) (a) A. A. Griswold and P. S. Starcher, *J. Org. Chem.*, **31**, 357 (1966); (b)

G. B. Bachman and T. Hokama, *ibid.*, **25**, 178 (1960); (c) D. Sheehan and A. F. Vellturo, U.S. Patent 3,574,756 (1971).
(5) K. K. Babievskii, V. M. Belikov, and N. A. Tikhonova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1161 (1970); *Dokl. Akad. Nauk SSSR*, **193**, 1055 (1970).
(6) K. K. Babievskii et al., *Dokl. Akad. Nauk SSSR*, **186**, 1079 (1969).
(7) T. Simmons and K. L. Kreuz, *J. Org. Chem.*, **33**, 836 (1968).
(8) H. Feuer and P. M. Pivawer, *J. Org. Chem.*, **34**, 2917 (1969).
(9) R. G. Pearson, D. H. Anderson, and L. L. Alt, *J. Am. Chem. Soc.*, **77**, 527 (1955).
(10) L. Claisen and E. Haase, *Chem. Ber.*, **33**, 1242 (1900).
(11) (a) J. B. Stothers and E. Y. Spenser, *Can. J. Chem.*, **39**, 1389 (1961); (b) R. R. Fraser and D. E. McGreer, *ibid.*, **39**, 505 (1961); (c) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2886 (1960).
(12) The stereochemistry of the compounds of ref 11a and 11b has been presented erroneously in a subsequent compilation.[13]
(13) W. Brügel, "Nuclear Magnetic Resonance Spectra and Chemical Structure", Vol. 1, Academic Press, New York, N.Y., 1967, p 145.
(14) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).
(15) Distillation was carried out without a fractionating column. No attempt was made at quantitative recovery of **6b**. The distillation residue contained **9b** in much larger quantities than present in the initial charge, indicating decomposition of **6b** to **9b**. Attempted distillation of **6b** on a larger scale resulted in extensive decomposition to **9b**.
(16) H. Feuer, H. B. Hass, and K. S. Warren, *J. Am. Chem. Soc.*, **71**, 3078 (1949).

Deuterium Isotope Effects and the Influence of Solvent in the Redox and Rearrangement Reactions of 2-Picoline *N*-Oxide and Phenylacetic Anhydride[1]

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Received May 20, 1975

The reaction of 2-picoline *N*-oxide with phenylacetic anhydride proceeds by two paths: rearrangement to produce picolyl phenylacetate (**6**), 2-(β-phenylethyl)pyridine (**7**), other minor rearrangement products, and CO_2, and oxidation to give benzaldehyde, 2-picoline, and CO_2. The ratio of the competing processes is sensitive to the incorporation of deuterium at appropriate sites in the reactants, thereby permitting a convenient method for determining hydrogen isotope effects. For rearrangement, a primary kinetic isotope effect value (3.8–4.2) is obtained when reactions of methyl-deuterated and undeuterated 2-picoline *N*-oxide are compared, confirming earlier work on related systems that anhydro base (**5**) formation is rate determining. Oxidation, however, manifests an inverse isotope effect (0.76–0.81, deuterium labeling at the methylene groups of phenylacetic anhydride) which, along with other evidence, suggests reversible enol or enolate formation prior to an SN1′-like rate-determining step to generate the reactive carbocation **3** or its conjugate base. Solvent polarity also significantly, but not dramatically, affects the ratio of the competing pathways. A trend is established which supports the proposed mechanisms if they are modified to include ion pairing phenomena. Furthermore, the influence of solvent polarity is found to be consistent with a dual mode of fragmentation of anhydro base intermediate **5**.

For over two decades there has been considerable interest in both the mechanistic and synthetic aspects of the reactions of carboxylic acid derivatives with the *N*-oxides of pyridine and picoline. The four-electron oxidative decarboxylation of anhydrides (or a mixture of the corresponding acid and acetic anhydride) which possess an acidic α hydrogen by pyridine *N*-oxide produces aldehydes or ketones, carbon dioxide, and pyridine as major products.[2-5] For example, the oxidation of phenylacetic anhydride by pyridine *N*-oxide produces benzaldehyde and proceeds according to the following stoichiometry.

$$(PhCH_2CO)_2O + 2C_5H_5NO \rightarrow PhCHO + 2C_5H_5N + CO_2 + PhCH_2CO_2H$$

The reaction is thought[2-5] to involve acylation of pyridine *N*-oxide, probably reversibly,[6] to yield the *N*-acyloxypyridinium ion **1** (R = H) (Scheme I). The latter cation, by reaction with a second molecule of pyridine *N*-oxide and loss of a pyridine molecule, is then believed to produce the intermediate *N*-(α-carboxybenzyloxy)pyridinium ion **4** (R = H) or the corresponding carboxylate zwitterion.[2,5] Decarboxylative fragmentation of **4** (R = H) (or its conjugate base) as shown would yield benzaldehyde, carbon dioxide, and pyridine.[7]

Although there is substantial evidence for the intermediate **4** (or its conjugate base),[5,8a] the mechanism of the conversion of **1** to **4** is not entirely clear. It has been suggested[2,4,5,8a] that pyridine is displaced from the enol **2** (R = H) of **1** (R = H) by pyridine *N*-oxide in an SN1′ or SN2′ manner. Enolization is consistent with the requirement for an α hydrogen atom.[2b,3c,5] On the basis of the experimental finding that pyridine *N*-oxide is much more nucleophilic than pyridine toward the intermediate, an SN1′ attack involving the α-carboxybenzylcarbenium ion **3**, or its conjugate base, has been favored.[8a] Some such electrophilic intermediate has been trapped by acetic acid and by pyridine, each utilized as solvent.[5] Further evidence for a cationic intermediate of type **3** has been found in the oxidation of 2,3-diphenylpropanoic acid by pyridine *N*-oxide;[8b] in addition to attack by *N*-oxide to ultimately yield the expected oxidation product, the reactive electrophilic species undergoes loss of an adjacent proton to produce an α,β-unsaturated carboxylic acid and it is also attacked by acetate to give the 2-acetoxy derivative of the starting acid.

The reaction of 2-picoline *N*-oxide with phenylacetic anhydride yields, by a similar path, the products of oxidative decarboxylation, benzaldehyde, carbon dioxide, and 2-picoline (Scheme I, R = Me). By an alternative path, the rearrangement products 2-pyridylmethyl phenylacetate (**6**), 3- and 5-phenylacetoxy-2-picoline, 2-(β-phenylethyl)pyridine (**7**), and 3- and 5-benzyl-2-picoline are also obtained[9] (Scheme I). The rearrangement process is thought to pro-