α-Nitro Ketones. 3.[1] Stereochemistry of the Nitration of 1-Acetoxycyclohexenes:[2] Synthesis of 2-Nitrocyclohexanones

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The nitration of enol acetates of substituted cyclohexanones in acetic anhydride at 15 °C with concentrated nitric acid is a kinetically controlled process which can lead to cis–trans-substituted 2-nitrocyclohexanones in very good yields. The stereochemistry of the reaction is controlled by the transition-state geometry which resembles the enol acetate. The following 2-nitrocyclohexanones were prepared from the corresponding cyclohexanones via the enol acetates: 4-methyl, 4-ethyl, 4-isopropyl, 4-*tert*-butyl, 3-methyl, 3-*tert*-butyl, 5-methyl, 5-*tert*-butyl, 3,3,5-trimethyl, 3,5,5-trimethyl, 3,3,5,5-tetramethyl, and 2-methyl-4-*tert*-butyl.

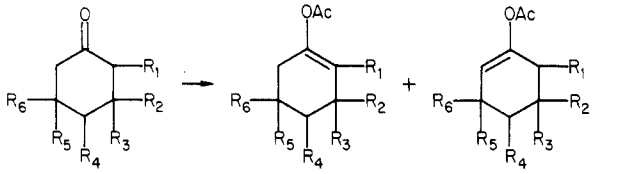
The synthetic uses of aliphatic nitro compounds have been well documented in recent reviews,[4] and many of these compounds[5,6] are readily available. The dual functionality of α-nitro ketones as well as the activating influence of the carbonyl group and nitro group on the adjacent carbons makes these compounds attractive synthetic intermediates. The preparation, chemical properties, and reactions of cyclic α-nitro ketones have also been recently reviewed.[6] Of the methods available for the synthesis of α-nitrocyclohexanones, the nitration of the enol esters of cyclohexanone appears to be an attractive method of preparation.[7] Although there are reports on optimizing the yield of 2-nitrocyclohexanone, a key intermediate in the synthesis of lysine, few other examples of the nitration of cyclic enol esters are known. As part of our study on the chemistry of α-nitro ketones we report on the stereochemistry of the nitration of 1-acetoxycyclohexenes and demonstrate the usefulness of the reaction for the preparation of substituted 2-nitrocyclohexanones.

Results

The enol acetates (**2** and **3**) used in this investigation were prepared by the acid-catalyzed reaction of the cyclohexanone with either acetic anhydride, which gives the thermodynamically more stable enol acetate,[8] or with isopropenyl acetate, which usually yields the less highly substituted isomer as the major product.[9] The unsymmetrical cyclohexanones (**1e–g,i**) yielded two isomeric enol acetates which were either nitrated as a mixture or separated by GLC and then nitrated separately. Table I lists the ketones and enol acetates used in this work.

Griswald and Starcher[10] had investigated the addition of acetyl nitrate to cyclohexanone enol acetate and proposed a mechanism involving the electrophilic addition of NO_2^+ to the enol ester to form an intermediate which could then break down to 2-nitrocyclohexanone via three pathways (Scheme I). In path A, the intermediate formed can lose a proton and form the β-nitrovinyl acetate. The reprotonation and hydrolysis of the β-nitrovinyl acetate would give the 2-nitrocyclohexanone. If this pathway predominates, then the stereochemistry of the initial attack of the electrophilic nitrating species would be lost. Formation of the 2-nitrocyclohexanone via pathways B and C, however, would not change the initial stereochemistry. To determine if pathway A was a possibility, we prepared the 1-acetoxy-2-nitro-3,3,5,5-tetramethylcyclohexene by refluxing the corresponding 2-nitro ketone with acetic anhydride and *p*-toluenesulfonic acid. Both 2-nitro- and 6-nitro-1-acetoxy-3,3,5,5-tetramethylcyclohexene were obtained and were separated by fractional crystallization.

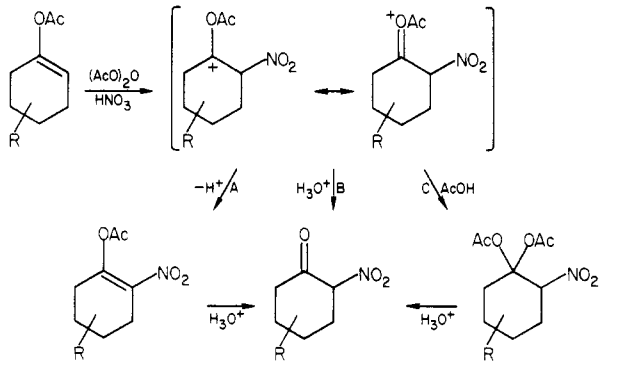
Table I. Enol Acetates of Substituted Cyclohexanones



1 **2** **3**

reaction	R_1	R_2	R_3	R_4	R_5	R_6
1a ⟶ 2a = 3a	H	H	H	CH_3	H	H
1b ⟶ 2b = 3b	H	H	H	CH_3CH_2	H	H
1c ⟶ 2c = 3c	H	H	H	$(CH_3)_2CH$	H	H
1d ⟶ 2d = 3d	H	H	H	$(CH_3)_3C$	H	H
1e ⟶ 2e + 3e	H	CH_3	H	H	H	H
1f ⟶ 2f + 3f	H	$(CH_3)_3C$	H	H	H	H
1g ⟶ 2g + 3g	H	CH_3	H	H	CH_3	CH_3
1h ⟶ 2h = 3h	H	CH_3	CH_3	H	CH_3	CH_3
1i ⟶ 2i + 3i	CH_3	H	H	$(CH_3)_3C$	H	H

Scheme I. Pathways for the Formation of 2-Nitrocyclohexanones



cis/trans

(1) Part 2. H. Özbal and W. W. Zajac, Jr., *J. Org. Chem.*, **45**, 4154 (1980).
(2) Presented at the 172nd Meeting of the American Chemical Society, Sept 1979, Washington, DC.
(3) Abstracted in part from the Ph.D. Thesis of H.Ö., Villanova University, Villanova, PA.
(4) (a) D. Seebach, E. W. Colvin, F. Lehr, and T. Weller *Chimia*, **33**, 1 (1979); J. Kochany, *Wiad. Chem.* **32**, 723 (1978).
(5) (a) 1-Nitrocyclohexene, E. J. Corey and H. Estreicher, *J. Am. Chem. Soc.*, **100**, 6294 (1978); (b) Nitroacetic acid esters, M. Schipchandler, *Synthesis*, 666 (1979).
(6) R. H. Fisher and H. M. Weitz, *Synthesis*, 261 (1980).
(7) D. Sheenan and A. F. Vellturo (Techni-Chem Co.), South African Patent 6 705 789, *Chem. Abstr.* **70**, 57261 (1969).
(8) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341, 2502 (1965).
(9) H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963).
(10) A. A. Griswold and P. S. Starcher, *J. Org. Chem.*, **31**, 357 (1966).

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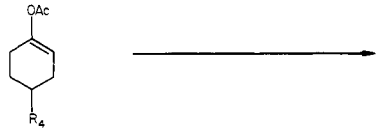
Table II. Isomer Distribution of 2-Nitrocyclohexanones

	% cis isomer		% trans isomer		
	kinetic	equilibrium	kinetic	equilibrium	% yield
					
		4		5	
2a, $R_4 = CH_3$	40	85	60	15	83
2b, $R_4 = CH_3CH_2$	45	85	55	15	92
2c, $R_4 = (CH_3)_2C$	45	88	55	12	85
2d, $R_4 = (CH_3)_3C$	48	91	52	9	75
					
		4		5	
2e, $R_2 = CH_3$; $R_5 = R_6 = H$	<1	<1	>99	>99	71[a]
2f, $R_2 = (CH_3)_3C$; $R_5 = R_6 = H$	<1	<1	>99	>99	70
2g, $R_2 = R_5 = R_6 = CH_3$	50	2	50	98	85
					
		6		7	
3e, $R_2 = CH_3$; $R_5 = R_6 = H$	50	10	50	90	71[a]
3f, $R_2 = (CH_3)_3C$; $R_5 = R_6 = H$	50	2	50	98	76
3g, $R_2 = R_5 = R_6 = CH_3$	71	10	26	90	87

[a] Total yield of 4–6 and 7e.

When 1-acetoxy-2-nitro-3,3,5,5-tetramethylcyclohexene was treated with acetic anhydride and nitric acid at 20 °C, under the normal nitration conditions, it was recovered unreacted. Addition of excess acid, prolonged reaction times, and temperatures up to 100 °C did not convert the 1-acetoxy-2-nitrocyclohexene to the corresponding 2-nitrocyclohexanone. From this observation, one could rule out pathway A, which involves the intermediacy of a 1-acetoxy-2-nitrocyclohexene, and be assured that the original stereochemistry does not change.

Another factor which had to be taken into consideration about the stereochemistry of the initial nitration product was the stability of the 2-nitro ketones. It is well-known that the α-protons of 2-nitro ketones are labile, and keto–enol tautomerism is possible.[11,12] The enol form of the 2-nitro ketones can readily be observed by NMR after being heated with acid or after being heated to about 100 °C. This could mean that the initial stereochemistry and thus the isomeric distribution could change by equilibrating via the enolic forms to the thermodynamically more stable isomer.

Treatment of 2-nitrocyclohexanone with DCl in D_2O at room temperature caused a complete disappearance of the α-proton signal in the NMR in about 2 days. At lower temperatures, the exchange rate was much slower. In this study, the initial isomeric distributions of the 2-nitrocyclohexanones, whose configurations we had previously reported,[1] were determined by the integration of the areas of the α-proton peaks. These determinations were made after the removal of excess acetic anhydride, residual acetic acid, and acetyl nitrate from the reaction mixture at temperatures of 30–40 °C and under reduced pressures before the final purification of the product and presumably before the equilibration had begun to occur. The NMR spectra on such crude products showed no absorption due to an enolic proton which ensured an accurate determination of the kinetic isomer distribution. Equilibration was readily achieved by the addition of a few drops of pyridine to the NMR tube.

The results of the stereochemistry of the addition of acetyl nitrate to the various enol acetates studied are summarized in Table II.

Discussion

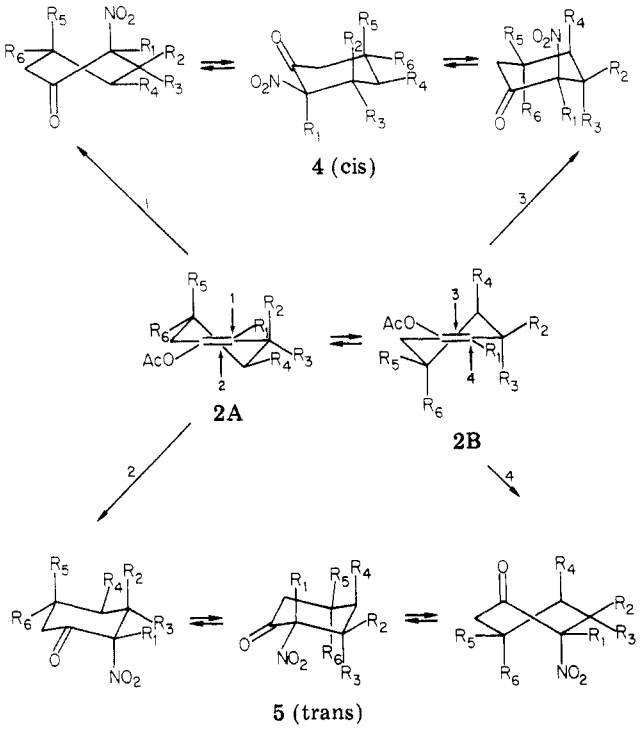
The results indicate that the reaction is kinetically controlled and need not give the thermodynamically more stable isomer as the major product. To be able to account for the isomeric distribution one also needs to consider the equilibria between the enol acetates, A ⇌ B. For the purposes of discussion, the enol acetates are divided into four classes according to the position of the alkyl substituents on the ring.

Nitration of Group I Enol Acetates. Group I enol acetates (**2a–d**) have an alkyl substituent only at position 4 and yield the thermodynamically less stable trans isomers in greater proportion in the kinetic mixtures which equilibrate to the more stable cis isomers. The ratio of the cis to trans isomers approaches unity as the size of the alkyl substituent at the 4-position gets larger from methyl to *tert*-butyl.

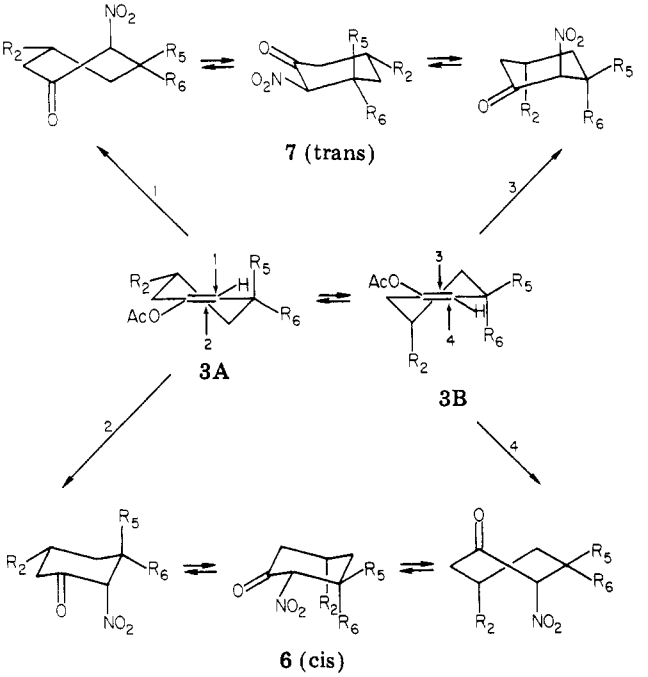
It is possible to explain the isomeric distribution of the kinetic mixture when one considers the four pathways available for the nitrating species to attack the equilibrating enol acetates as shown in Scheme II. As the size of the alkyl substitutent at the 4-position is changed from methyl to *tert*-butyl, the concentration of conformer B of the enol acetates decreases due to the reluctance of the bulky *tert*-butyl group to adopt the axial orientation.

(11) H. Feuer and P. M. Pivawer, *J. Org. Chem.*, 31, 3152 (1966).
(12) T. Simmons, R. F. Love, and K. L. Kreutz, *J. Org. Chem.*, 31, 2400 (1966).

Scheme II. Nitration of Group I, Group II, and Group IV Enol Acetates



Scheme III. Nitration of Group III Enol Acetates



Therefore, when the R_4 group is *tert*-butyl, only the enol acetate conformer A can be expected to be present. Formation of nearly equal amounts of cis and trans isomers in the kinetic mixture indicates that both nitration pathways 1 and 2 are energetically similar. This also suggests that the transition state comes early in the reaction coordinate with a geometry similar to that of the enol form rather than the ketone chair or twist boat.

As the size of the substitutent at the 4-position gets smaller, the concentration of enol acetate conformer B increases and opens pathways 3 and 4 for nitration. However, pathway 3 is less likely for nitration since the axial R_4 alkyl group hinders the approach of the nitrating species. This allows for a second pathway for the formation of the trans isomer which accounts for the increase in the amount of trans isomer in the kinetic mixtures as the R_4 group becomes smaller.

Nitration of Group II Enol Acetates. Nitration of the group II enol acetates (**2e–g**) yields the thermodynamically more stable trans isomers in the kinetic mixtures. However, this is not because the reaction is equilibrium controlled but because the pathways leading to formation of the cis isomers are energetically less favorable due to steric hindrance of the various alkyl groups. As shown in Scheme II, the enol acetate **2f** with a *tert*-butyl group exists mainly as conformer A and the large group also blocks nitration via pathway 2. Thus since only pathway 1 is available, the kinetic mixture yields only the trans product. In the case of the enol acetate **2e** with a methyl group at the 3-position, the concentration of both conformers at equilibrium is high. However, in this case also, for nitration, only pathways 1 and 3 are the most favorable, yielding again the trans product. The conformational equilibrium of enol acetate **2g** should lie far to the side of conformer A because of the steric interactions between axial and pseudoaxial methyl groups in conformer B. The nearly equal amounts of cis and trans isomer distribution, however, can be accounted for by the high concentration of conformer A but restricted nitration via pathway 1 because of axial CH_3, and unlike enol acetates **2e** and **2f**, pathway 2 now becomes competitive, which leads to the formation of cis isomer.

Nitration of Group III Enol Acetates. Nitration of group III enol acetates (**3e–g**) is shown in Scheme III and follows the similar pattern observed for groups I and II.

In the nitration of enol acetate **3f** with a very low concentration of conformer B due to the bulky *tert*-butyl group, the expected equal distribution of cis and trans isomers is observed. The accurate determination of isomeric distribution from the nitration of enol acetate **3e** could not be determined accurately due to extensive overlap of the α-proton resonances; however, the ratio was estimated to be about 1:1. For the nitration of enol acetate **3g** conformer A should predominate due to axial–pseudo axial steric repultions between the methyl groups. Under these conditions, nitration of **3g** would proceed only via pathways 1 and 2. Pathway 1 should be less favorable due to the interation of the nitrating species and an axial methyl group. Pathway 2 leading to the cis isomer should be preferred and lead to a preponderance of the trans isomer, which is observed experimentally. The members of this group also equilibrated to the thermodynamically more stable trans isomers.

Nitration of Group IV Enol Acetate. The only compound in this group, 1-acetoxy-2-methyl-4-*tert*-butylcyclohexene (**2i**), yielded 2-nitro ketones with no α-proton, thus eliminating the possibility of equilibration through an enol.

The distribution of the isomers was determined by integration of the area under the axial and equatorial 2-methyl resonances. The singlet observed at δ 1.61 was assigned to the axial 2-methyl group and the one at δ 1.85 to the equatorial. The assignment of stereochemistry was initially based upon the work of Kuehne.[13] This assignment of configuration was confirmed by the methylation of the potassium salt of 2-nitro-4-*tert*-butylcyclohexanone which led to the isomer with the methyl group in the axial position.

The enol acetate **2i** ($R_1 = CH_3$, $R_4 = (CH_3)_3C$) would be expected to exist only as conformer A with the *tert*-butyl

(13) M. E. Kuehne, *J. Org. Chem.*, **35**, 171 (1970).

group equatorial (Scheme II). Only pathways 1 and 2 are then available for product formation. Unlike group I enol acetates with a substituent at position 4 which give approximately a 1:1 cis/trans ratio of 2-nitro ketones, introduction of the methyl group at position 2 leads to predominantly one isomer (9:1) with the nitro group axial. Furthermore, the reaction of the 2-methyl enol acetate proceeded sluggishly and was accompanied by cleavage products.[12,14,15]

These results may be explained in the following manner. The substituent at position two which slows down the reaction causes bond formation to occur late along the reaction coordinate and have a transition-state geometry resembling that of the ketone, unlike group I–III enol acetate reactions in which the transition state occurs early. Attack via pathway 1 leading to the equatorial nitro group would have to proceed through a chairlike transition state, and the nitro group is introduced preferentially axially.

In conclusion, we have demonstrated not only that the nitration of enol acetates leads to products with stereochemistry kinetically established but also that the nitration of enol acetates of cyclohexanones substituted in any position, except position 2, is a synthetically useful reaction producing substituted 2-nitrocyclohexanones in very good yields. The application of this reaction to the synthesis of 2-nitrocyclopentanones will be reported in a subsequent publication.

Experimental Section

The ^1H NMR spectra were determined on either a Varian Associates A-60, HA-100 or HA-220 spectrometer. Samples were dissolved in $CDCl_3$ with tetramethylsilane as an internal standard. The proton chemical shifts are presented in parts per million (δ) downfield from the internal standard (Me_4Si). All melting points were determined on a Thomas-Hoover capillary melting point apparatus. All gas chromatographic determinations were carried out on a Hewlett-Packard, F&M Scientific Model 700 gas chromatograph equipped with a thermal-conductivity detector. The elemental analyses were performed by Galbraith Laboratories, Inc.

2-Nitro-4-methylcyclohexanone (Cis–Trans Mixture, 4a and 5a). A mixture of 3.08 g (20 mmol) of 1-acetoxy-4-methylcyclohexene[9] and 7.0 g (68 mmol) of acetic anhydride was placed into a three-necked, 50-mL, round-bottomed flask equipped with a magnetic stirrer, an addition funnel and a thermometer. Concentrated nitric acid (1.4 mL, 22 mmol) was added dropwise to the stirred solution, and the temperature of the solution was kept between 15 and 20 °C. After the addition was completed, the yellow-green solution was allowed to stir for 1 h at about the same temperatures. The residual acetyl nitrate, acetic acid, and excess acetic anhydride were removed by vacuum distillation with pot temperatures not exceeding 40 °C. The cis/trans ratio of the crude product was 40:60. The crude product (3.06 g, 97%) was purified by vacuum distillation, and 2.62 g (83%) of clear, yellow liquid was obtained: bp 85–88 °C (0.2 torr); ^1H NMR ($CDCl_3$) δ 1.24 (2 d, 3 H, CH_3), 1.5–2.9 (m, 7 H, ring protons), 5.16 (dd, $CHNO_2$, trans isomer), 5.41 (dd, $CHNO_2$, cis isomer).

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.04; N, 8.91. Found: C, 53.61; H, 7.27; N, 9.01.

2-Nitro-4-ethylcyclohexanone (Cis–Trans Mixture, 4b and 5b). A mixture of 6.85 g (40 mmol) of 1-acetoxy-4-ethylcyclohexene[9] and 14.0 g (136 mmol) of acetic anhydride was placed in a 50-mL, round-bottomed flask equipped with a magnetic stirrer and a thermometer. Concentrated nitric acid (2.85 mL, 44 mmol) was added dropwise to the stirred solution, during which the temperature was maintained between 15 and 20 °C. After an additional hour of stirring at about the same temperatures, residual acetyl nitrate, acetic acid, and excess acetic anhydride were removed under reduced pressures with a maximum pot temperature of 40 °C. The cis/trans ratio of the crude product was 40:60. The crude product was purified by vacuum distillation, and 6.35 g (92%) of clear, yellow product was obtained: bp 100–108 °C (0.3–0.4 torr); ^1H NMR ($CDCl_3$) δ 0.90–1.14 (m, 5 H, CH_2CH_3), 1.19–2.81 (m, 7 H, ring protons), 5.29 (dd, $CHNO_2$, trans isomer), 5.44 (dd, $CHNO_2$, cis isomer).

Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.08; H, 7.74; N, 7.95.

2-Nitro-4-isopropylcyclohexanone (Cis–Trans Mixture, 4c and 5c). A mixture of 5.1 g (28 mmol) of 1-acetoxy-4-isopropylcyclohexene[8] and 10.0 g (98 mmol) of acetic anhydride was placed in a 50-mL, round-bottomed flask equipped with a magnetic stirrer and a thermometer. Concentrated nitric acid (2.0 mL, 32 mmol) was added dropwise to the stirred solution, during which the temperature was maintained between 15 and 22 °C. After an additional 3 h of stirring at about the same temperatures, the residual acetyl nitrate, acetic acid, and the excess acetic anhydride were removed under reduced pressures with a maximum pot temperature of 40 °C. The cis/trans ratio of the crude product was 45:55. The crude product was purified by vacuum distillation, and 4.4 g (85%) of clear yellow product was obtained: bp 116–119 °C (0.8–0.9 torr); ^1H NMR ($CDCl_3$) δ 0.97 (d, 6 H, $CH(CH_3)_2$), 1.22–2.90 (m, 8 H, ring protons), 5.06 (dd, $CHNO_2$, trans isomer), 5.44 (dd, $CHNO_2$, cis isomer).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.02; H, 8.16; N, 7.73.

2-Nitro-4-*tert*-butylcyclohexanone (Cis–Trans Mixture, 4d and 5d). A mixture of 17.7 g (0.09 mol) of 1-acetoxy-4-*tert*-butylcyclohexene[8] and 32.3 g (0.31 mol) of acetic anhydride was placed in a round-bottomed flask equipped with a magnetic stirrer, a thermometer, and an addition funnel. Concentrated nitric acid (5.88 mL, 0.092 mol) was added dropwise to the stirred solution, during which the temperature was maintained between 15 and 20 °C. After an additional hour of stirring at about the same temperatures, the residual acetyl nitrate, acetic acid, and excess acetic anhydride were removed under reduced pressures with a maximum pot temperature of 40 °C. The cis/trans ratio of the crude product was 48:52. Upon being allowed to stand at room temperature for 3 h, the orange liquid solidified. After two crystallizations from methanol, 13.5 g (75%) of white crystals was obtained. The NMR of the crystals indicated that only the cis isomer was present. During crystallization, the thermodynamically less stable trans isomer equilibrated to the cis isomer.

Cis isomer: mp 87–90 °C; ^1H NMR ($CDCl_3$) δ 0.98 (s, 9 H, $C(CH_3)_3$), 1.15–2.70 (m, 7 H, ring protons), 5.37 (dd, 1 H, $CHNO_2$).

Trans isomer: could not be isolated; ^1H NMR ($CDCl_3$) δ 0.96 (s, 9 H, $C(CH_3)_3$), 4.98 (t, 1 H, $CHNO_2$).

Anal. Calcd for $C_{10}H_{17}NO_3$ (cis isomer): C, 60.31; H, 8.53; N, 7.03. Found: C, 60.16; H, 8.70; N, 6.81.

2-Nitro-3-methylcyclohexanone and 2-Nitro-5-methylcyclohexanone (Cis–Trans Mixtures, 4e, 5e and 6e, 7e). A mixture of 1.54 g (10 mmol) of a 50/50 mixture of 1-acetoxy-3-methylcyclohexene and 1-acetoxy-5-methylcyclohexene[9] and 3.5 g (34 mmol) of acetic anhydride was placed in 50-mL, round-bottomed flask equipped with a magnetic stirrer, thermometer, and an addition funnel. Concentrated nitric acid (0.7 mL, 11 mmol) was added dropwise to the stirred solution, during which the temperature was maintained between 15 and 20 °C. After the mixture was stirred an additional 2 h at about the same temperatures, the residual acetyl nitrate, acetic acid, and excess acetic anhydride were removed under reduced pressures with a maximum pot temperature of 40 °C to give 1.12 g (71%) of *cis*- and *trans*-2-nitro-3-methyl- and -5-methylcyclohexanones. The cis/trans isomer distribution of 2-nitro-3-methylcyclohexanone in the crude product was 2:98. The cis/trans isomer distribution of 2-nitro-5-methylcyclohexanone in the crude product could not be accurately determined due to extensive overlap but was approximately 50:50.

trans-2-Nitro-5-methylcyclohexanone (**7e**) solidified out of the reaction mixture when it was allowed to stand in an ice–water bath. Filtration and recrystallization twice from methanol yielded 0.78 g of white crystals: mp 82–85 °C; ^1H NMR ($CDCl_3$) δ 1.10 (d, 3 H, $CHCH_3$), 1.33–2.73 (m, 8 H, ring protons), 5.21 (dd, 1 H, $CHNO_2$).

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.04; N, 8.91. Found: C, 53.36; H, 7.26; N, 8.87.

(14) A. S. Matlack and D. S. Breslow, *J. Org. Chem.*, **32**, 1995 (1967).
(15) H. Feuer and P. M. Pivawer, *J. Org. Chem.*, **34**, 2917 (1969).

cis-2-Nitro-5-methylcyclohexanone (6e) could not be isolated.

trans-2-Nitro-3-methylcyclohexanone (5e) could be obtained in pure form by column chromatography on 50 g of silica gel. A mixture of methylene chloride/hexane (1:5) was used as eluent, and 250-mL fractions were collected. Fractions 50–60 contained the pure *trans*-2-nitro-3-methylcyclohexanone. The compound was recrystallized from methanol and white crystals were obtained: mp 64–65.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3 H, $CHCH_3$), 1.30–2.83 (m, 8 H, ring protons), 5.07 (d, 1 H, $CHNO_2$).

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.04; N, 8.91. Found: C, 53.50; H, 6.99; N, 8.79.

***trans*-2-Nitro-3-*tert*-butylcyclohexanone (5f).** A mixture of 0.5 g (2.5 mmol) of 1-acetoxy-3-*tert*-butylcyclohexene[9] and 3.5 g (34 mmol) of acetic anhydride was placed in a 15-mL, round-bottomed flask equipped with a magnetic stirrer and a thermometer. Concentrated nitric acid (0.3 mL, 4.8 mmol) was added dropwise to the stirred solution, during which the temperature was maintained between 15 and 20 °C. After an additional hour of stirring at about the same temperatures, the residual acetyl nitrate, acetic acid, and excess acetic anhydride were removed under reduced pressures with a maximum pot temperature of 40 °C. Upon being allowed to stand at room temperature, the remaining yellow solution solidified. Recrystallization twice from methanol yielded 0.35 g (70%) of white crystals: mp 78–79 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 9 H, $C(CH_3)_3$), 1.20–2.80 (m, 8 H, ring protons), 5.20 (d, 1 H, $CHNO_2$).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.59; N, 7.03. Found: C, 60.55; H, 8.71; N, 7.07.

2-Nitro-5-*tert*-butylcyclohexanone (Cis–Trans Mixture, 6f and 7f). A mixture of 0.7 g (3.5 mmol) of 1-acetoxy-5-*tert*-butylcyclohexene[9] and 4.0 g (4.0 mmol) acetic anhydride was placed in a 15-mL, round-bottomed flask equipped with a magnetic stirrer and a thermometer. Concentrated nitric acid (0.4 mL, 6.3 mmol) was added dropwise to the stirred solution, during which the temperature was maintained between 15 and 20 °C. After an additional hour of stirring, the residual acetyl nitrate and acetic acid and excess acetic anhydride were removed under reduced pressures with maximum pot temperature of 35 °C. The cis/trans ratio of the crude product was 50:50. The remaining yellow oily liquid (0.53 g, 76%) could not be crystallized from various solvents: ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 9 H, $C(CH_3)_3$), 1.25–2.87 (m, 8 H, ring protons), 4.91 (dd, $CHNO_2$, cis isomer), 5.39 (dd, $CHNO_2$, trans isomer).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.59; N, 7.03. Found: C, 60.72; H, 8.27; N, 7.30.

2-Nitro-3,5,5-trimethylcyclohexanone (Cis–Trans Mixture, 4g and 5g). A mixture of 2.0 g (11 mmol) of 1-acetoxy-3,5,5-trimethylcyclohexene[9] and 3.5 g (35 mmol) of acetic anhydride was placed in a 15-mL, round-bottomed flask equipped with a magnetic stirrer and a thermometer. Concentrated nitric acid (0.7 mL, 11 mmol) was added dropwise to the stirred solution, during which the temperature was maintained at 15–20 °C. After an additional hour of stirring at about the same temperatures, the residual acetyl nitrate, acetic acid, and excess acetic anhydride were removed under reduced pressures with a maximum pot temperature of 45 °C. The cis/trans ratio of the crude product was 50:50. The cis isomer could not be isolated and readily equilibrated to the trans isomer. The pure trans isomer, 1.67 g (84%), was obtained by crystallization from methanol, and white crystals were obtained: mp 92.5–93.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 and 1.13 (s, 6 H, $C(CH_3)_2$), 1.10 (d, 3 H, $CHCH_3$), 1.63 (m, 2 H, protons on C-4), 2.33 (s, 2 H, protons on C-6), 2.78 (m, 1 H, $CHCH_3$), 4.92 (d, $CHNO_2$, trans isomer), 4.93, (d, $CHNO_2$, cis isomer).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.52; H, 8.04; N, 7.48.

2-Nitro-3,3,5-trimethylcyclohexene (Cis–Trans Mixture, 6g and 7g). A mixture of 2.0 g (11 mmol) of 1-acetoxy-3,3,5-trimethylcyclohexene[9] and 3.5 g (35 mmol) of acetic anhydride was placed in a 15-mL, round-bottomed flask equipped with a magnetic stirrer and a thermometer. Concentrated nitric acid (0.7 mL, 11 mmol) was added dropwise to the stirred solution, during which the temperature was maintained between 15 and 20 °C. After an additional hour of stirring at about the same temperature, the residual acetyl nitrate, acetic acid, and excess acetic anhydride were removed under reduced pressures with a maximum pot temperature of 45 °C. The cis/trans ratio of the crude product was 75:25. The cis isomer could not be isolated and readily equilibrated to the trans isomer. The pure trans isomer (1.75 g, 88%) was obtained by crystallization from methanol, and white crystals were obtained: mp 48.5–49 °C; ^{1}H NMR ($CDCl_3$) δ 0.90–1.13 (m, $CHCH_3$, 1.14 (s, 6 H, $C(CH_3)_2$), 1.30–2.80 (m, 5 H, ring protons), 4.62 (s, $CHNO_2$, cis isomer), 5.26 (s, $CHNO_2$, trans isomer).

Anal. Calcd for $C_9H_{15}NO_{13}$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.39; H, 8.04; N, 7.51.

***cis*-2-Nitro-2-methyl-4-*tert*-butylcyclohexanone.** Concentrated nitric acid (2.5 mL, 0.040 mol) was added dropwise to a stirred mixture of 1-acetoxy-2-methyl-4-*tert*-butylcyclohexene (7.35 g, 0.035 mol) and acetic anhydride (14.3 g, 0.140 mol) at 15–20 °C. The green solution was allowed to stir at approximately the same temperature for 2 h and then was distilled in vacuo, keeping the bath temperature below 50 °C, to remove residual acetyl nitrate, acetic acid, and excess acetic anhydride. Attempts to crystallize the crude product in common solvents were not successful. Therefore, the crude oil was distilled, and three fractions were collected. The first fraction [bp 82–87 °C (1.2 torr)] was 2-methyl-4-*tert*-butylcyclohexanone, the third fraction [bp 124–130 °C (1.2 torr)] was *trans*-2-nitro-2-methyl-4-*tert*-butylcyclohexanone (1.34 g, 18%), and the second fraction [bp 95–105 °C (1.2 torr)] was a mixture of the two components. The third fraction, a light yellow liquid, crystallized upon standing overnight at room temperature. After recrystallization from an ethanol and ether mixture, a colorless solid was obtained: mp 83–84 °C; ^{1}H NMR ($CDCl_3$) 0.96 (s, 9 H, $C(CH_3)_3$), 1.61 (s, 3 H, CH_3), 1.14–2.94 (m, 7 H, ring protons).

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.97; H, 8.92; N, 6.57. Found: C, 62.73; H, 9.16; N, 6.35.

***trans*-2-Nitro-2-methyl-4-*tert*-butylcyclohexanone.** The potassium salt of 2-nitro-4-*tert*-butylcyclohexanone (1.70 g, 7.0 mmol) prepared by the method reported in the literature[13] was suspended in a mixture of 20 mL of dry benzene and 6 mL of dimethylformamide in a 50-mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser. The flask was immersed in an ice–water bath, and 5.0 g (35 mmol) of methyl iodide was added all at once to the stirred solution. The mixture was allowed to come to room temperature and was stirred overnight. The reaction mixture was then poured into 250 mL of iced dilute sodium hydroxide solution and extracted three times with 50-mL portions of ether. The combined ether extracts were washed with saturated salt solution, dried over $MgSO_4$, and concentrated. The residual oil was crystallized from ether at low temperatures, and 0.35 g (23%) of white crystals was obtained: mp 120–122 °C; ^{1}H NMR ($CDCl_3$) 1.00 (s, 9 H, $C(CH_3)_3$), 1.85 (s, 3 H, CH_3), 1.30–2.80 (m, 7 H, ring protons).

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.97; H, 8.92; N, 6.57. Found: C, 62.15; H, 8.79; N, 6.49.

2-Nitro-3,3,5,5-tetramethylcyclohexanone. A mixture of 29.4 g (0.15 mol) of 1-acetoxy-3,3,5,5-tetramethylcyclohexene[9] and 53.0 g (0.5 mol) of acetic anhydride was placed in a round-bottomed flask equipped with a magnetic stirrer, a thermometer, and an addition funnel. Concentrated nitric acid (10.0 mL, 0.16 mol) was added dropwise to the stirred solution, during which the temperature was maintained between 15 and 20 °C. After an additional hour of stirring at about the same temperature, the residual acetyl nitrate, acetic acid, and excess acetic anhydride were removed under reduced pressure with a maximum pot temperature of 45 °C. The remaining product solidified and was recrystallized from methanol: 25.0 g (85%); white crystals; mp 76–77 °C; ^{1}H NMR ($CDCl_3$) δ 1.09, 1.11, 1.18, and 1.25 (4 s, 12 H, four CH_3 groups), 1.81 (s, 2 H, protons on C-4), 2.43 (s, 2 H, protons on C-6), 5.21 (s, 1 H, $CHNO_2$).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.59; N, 7.03. Found: C, 60.27; H, 8.72; N, 7.00.

1-Acetoxy-2-nitro-3,3,5,5-tetramethylcyclohexene and 1-Acetoxy-6-nitro-3,3,5,5-tetramethylcyclohexene. A mixture of 3.0 g (0.015 mol) of 2-nitro-3,3,5,5-tetramethylcyclohexanone, 15.0 g (0.15 mol) of acetic anhydride, and 0.02 g of *p*-toluenesulfonic acid was heated at 110 °C in a 25-mL, round-bottomed flask equipped with magnetic stirrer and a condenser for 48 h. The solution turned black after 1 day. After the mixture cooled to room temperature, 50 mL of ether was added, and the solution

was washed three times with 25-mL portions of water, twice with 25-mL portions of 5% aqueous K_2CO_3, and finally with saturated salt solution. The organic layer was dried over $MgSO_4$ and concentrated.

1-Acetoxy-2-nitro-3,3,5,5-tetramethylcyclohexene was isolated by fractional crystallization from ether at low temperatures, and after recrystallization from ether 0.75 g of white crystals was obtained: mp 84–85 °C; ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 6 H, $C(CH_3)_2$), 1.43 (s, 6 H, $C(CH_3)_2$), 1.81 (s, 2 H, protons on C-4), 2.70 (s, 2 H, protons on C-6), 2.27 (s, 3 H, $COCH_3$).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.49; H, 7.93; N, 5.80. Found: C, 59.81; H, 8.33; N, 5.35.

The remaining liquid was distilled under reduced pressures and 1.33 g of clear yellow liquid of 1-acetoxy-6-nitro-3,3,5,5-tetramethylcyclohexene was obtained: bp 90–95 °C (0.4 torr); ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 3 H, CH_3), 1.19 (s, 6 H, $C(CH_3)_2$), 1.26 (s, 3 H, CH_3), 1.74 (s, 2 H, protons on C-4), 2.13 (s, 6 H, $COCH_3$), 4.78 (s, 1 H, $CHNO_2$), 5.67 (s, 1 H, olefinic proton).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.49; H, 7.93; N, 5.80. Found: C, 59.17; H, 7.65; N, 5.83.

Registry No. **1a**, 589-92-4; **1b**, 5441-51-0; **1c**, 5432-85-9; **1d**, 98-53-3; **1e**, 591-24-2; **1f**, 936-99-2; **1g**, 873-94-9; **1h**, 14376-79-5; **1i**, 5064-52-8; **2a**, 22422-17-9; **2b**, 77507-06-3; **2c**, 77507-07-4; **2d**, 7360-39-6; **2e**, 15786-53-5; **2f**, 77507-08-5; **2g**, 4883-56-1; **2h**, 56763-68-9; **2i**, 20826-66-8; **3e**, 22336-10-3; **3f**, 66464-47-9; **3g**, 5011-67-6; **4a**, 74609-67-9; **4b**, 74609-69-1; **4c**, 74609-71-5; **4d**, 74609-73-7; **4g**, 74609-81-7; **5a**, 74609-68-0; **5b**, 74609-70-4; **5c**, 74609-72-6; **5d**, 74609-74-8; **5e**, 74609-64-6; **5f**, 74609-66-8; **5g**, 74609-82-8; **6e**, 74609-75-9; **6f**, 74609-77-1; **6g**, 74609-79-3; **7e**, 74609-76-0; **7f**, 74609-78-2; **7g**, 74609-80-6; *trans*-2-nitro-2-methyl-4-*tert*-butylcyclohexanone, 77507-09-6; 2-nitro-4-*tert*-butylcyclohexanone K, 77507-10-9; 2-nitro-3,3,5,5-tetramethylcyclohexanone, 74609-83-9; 1-acetoxy-2-nitro-3,3,5,5-tetramethylcyclohexene, 77507-11-0; 1-acetoxy-6-nitro-3,3,5,5-tetramethylcyclohexene, 77507-12-1.

Catechol and Substituted Catechol-Derived Ortho Esters, Models for Protected Active Esters in Peptide Synthesis

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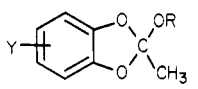
Monoalkyl orthoacetates derived from catechol, 4-nitrocatechol, and tetrabromocatechol have been prepared, and mild conditions (NaI–BF_3OEt_2) have been found that convert them to the corresponding catechol monoacetates in high yield. Possible applications of ortho esters as protected active esters for peptide synthesis are discussed.

In this paper we describe model studies of catechol-derived ortho esters 1 which demonstrate the potential application of these species as "safety-catch" protected active esters.



1

In 1968 Jones and Young[1] advanced the concept of safety-catch activation of carboxylic acids through their use of *o*-benzyloxyphenyl esters as blocked amide-forming reagents. Subsequently, Corvell and Jones have used these species for the synthesis of sequential polypeptides.[2] Because the *o*-benzyloxyphenyl esters are relatively inert to aminolysis under the usual conditions of peptide synthesis, they can be used as C-terminal blocking groups that are carried unchanged through several synthetic steps. Hydrogenolytic debenzylation generates a catechol monoester which can undergo rapid aminolysis resulting from anchimeric assistance by the phenolic hydroxyl group.

This ingenious amide-forming process has several intrinsic disadvantages, of which the most serious is the relatively low aminolytic reactivity of *o*-hydroxyphenyl esters, which confines their use to efficient couplings that can be run at relatively high concentrations or with unhindered amino acids. Introduction of electron-withdrawing groups to increase the rate of aminolysis of the *o*-hydroxyphenyl ester is also expected to increase the lability of the *o*-benzyloxyphenyl ester which is its precursor. A second problem is thus seen to be the benzyloxy function which is an imperfect safety catch that only masks hydroxyl catalysis and not the intrinsic ester reactivity.[3]

The ready formation of *o*-phenylene orthoacetate from a transketalization reaction between catechol and triethyl orthoacetate[4] and the availability of carbobenzyloxyglycine triethyl ortho ester[5] suggested the possibility of using an ortho ester as a safety catch for a catechol or substituted catechol monoester. Ortho esters as safety catches offer the potential advantage that they completely mask any ester reactivity. In addition, they are inert to a variety of neutral and/or basic conditions but are labile to acid. As in the case of urethane groups this acid lability can vary greatly depending on structure. Although the use of ortho esters in peptide synthesis would restrict the use of acid-labile amine protection, these species should be compatible with a variety of base-labile protective groups or those removed by hydrogenation. Three issues must be resolved before attempts can be made to apply ortho esters to the synthesis of large polypeptides. (1) Model systems must be prepared that demonstrate conditions that quantitatively convert catechol-derived ortho esters to the corresponding catechol monoesters. This demonstration may be relevant to many situations requiring a protected, activated carboxyl. (2) A general method must be found to

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