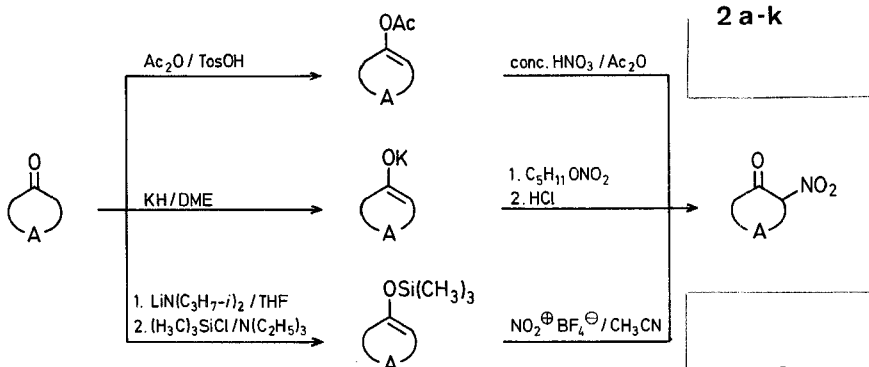


α -Nitro Ketones; 8¹. Nitration of Enol Acetates with Trifluoroacetic Anhydride and Ammonium Nitrate

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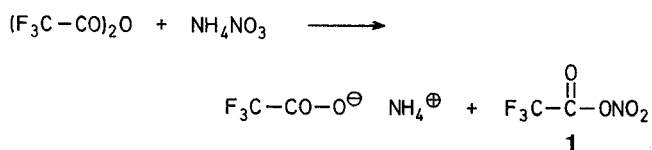
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There are three methods available for the synthesis of cyclic α -nitro ketones starting with the ketone: (1) nitration of the enol acetate with nitric acid^{3,4,5}; (2) nitration of the potassium enolate with pentyl nitrate^{6,7}; and (3) nitration of the silyl enol ether with nitronium tetrafluoroborate^{5,8}.



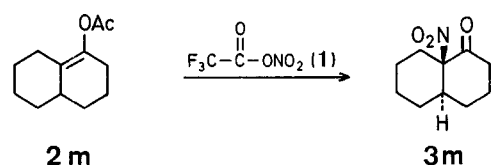
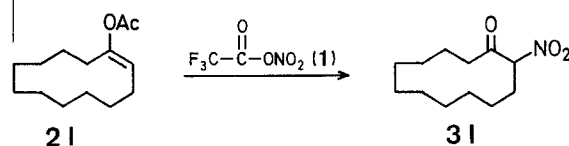
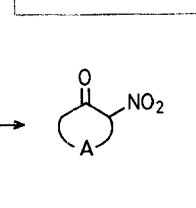
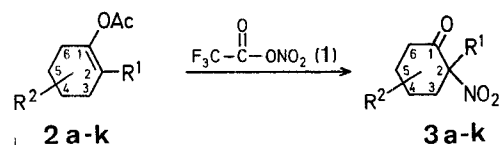
Unfortunately, 2-alkyl-2-nitrocyclohexanones cannot be prepared in acceptable yields by these methods. In fact, the enol acetate method is the only one that can be used but the yields are generally low and ring cleavage products are often the major products^{4,5,6}. Although 2-methyl-2-nitrocyclohexanones can also be prepared by phase-transfer methylation of 2-nitrocyclohexanones⁵, the ready availability of the thermodynamically more stable 2-substituted enol acetates from the 2-substituted cyclohexanones⁹ makes them attractive starting materials for 2-alkyl-2-nitrocyclohexanones if suitable conditions for nitration could be developed.

The nitration of enol acetates is a regioselective electrophilic addition to the β -carbon atom of the enol acetate followed by a hydrolytic conversion of the intermediate to the α -nitro ketone with its stereochemistry kinetically established. A methyl group at position 2 in the enol acetate decreases the rate of nitration and increases the ease of the ring opening reaction. When a mixture of nitric acid and acetic anhydride is the nitrating system, the electrophile generated is acetyl nitrate or its conjugate acid. Crivello¹⁰ has recently reviewed the use of inorganic nitrate salts and substituted acetic anhydrides for the nitration of aromatic compounds and demonstrated that ammonium nitrate and trifluoroacetic anhydride is the most effective nitrating mixture. Under the reaction conditions trifluoroacetyl nitrate (**1**) is produced, which is a much more powerful nitrating agent than acetyl nitrate.



Based upon these results the trifluoroacetyl nitrate method of nitration was attempted on enol acetates **2** of cyclic ketones. It was found in a preliminary experiment that addition of trifluoroacetic anhydride to a mixture of the enol acetate of 3,3,5,5-tetramethylcyclohexanone (**2k**) and ammonium nitrate in the absence of solvent at room temperature, led to a vigor-

ous reaction that was over in less than 1 min. In order to reduce the vigor of the reaction, chloroform was used as a solvent in subsequent experiments. Generally the reaction was complete within 10–20 min (i.e. when the ammonium nitrate had dissolved) and in most cases the ¹H-N.M.R. spectrum of the reaction mixture indicated that the α -nitro ketone **3** was the sole product. The enol acetates **2a–m** that were nitrated are listed in the Table.



Enol acetates without a substituent at C-2, (**2a, j, k, l**) yielded nitro ketones (**3a, j, k, l**) that were solids which could be crystallized after removal of the volatiles by rotary evaporation. Furthermore, the enol acetate of 4-*t*-butylcyclohexanone (**2j**) yielded the same kinetic ratio (3 : 2) of *cis* and *trans*-4-*t*-butyl-2-nitrocyclohexanones (**3j**) as did the acetyl nitrate nitration⁴. The most gratifying results were obtained from the nitration of enol acetates substituted at position 2 with a methyl group (**2b, c, d**) or a primary alkyl group such as ethyl, *n*-propyl, or *n*-butyl (**2e, f, g**). In each case an excellent yield of the corresponding 2-alkyl-2-nitrocyclohexanone (**2e–g**) was obtained and there was no evidence of ring cleavage products. This is in direct contrast to what is observed in acetyl nitrate nitration of the enol acetates of 2-alkylcyclohexanones. Attempts at nitrating enol acetates with other than primary alkyl groups at position 2 were not as successful. 2-*t*-Butyl-1-acetoxycyclohexene (**2i**) gave only an 18% yield of 2-*t*-butyl-2-nitrocyclohexanone (**3i**). The more substituted enol acetate of menthone (**2h**; isopropyl group at position 2) did not lead to the expected α -nitro ketone **3h** but to a mixture of products. However, the $\Delta^{1,9}$ -enol acetate of 1-decalone (**2m**) was quantitatively converted to *trans*-9-nitro-1-decalone (**3m**).

The ketones required for the preparation of the enol acetates **2** are commercially available from Aldrich. The enol acetates **2** were prepared by the reaction of the ketones with acetic anhydride in the presence of *p*-toluenesulfonic acid⁹. The physical constants and I.R. (Perkin-Elmer 299) and N.M.R. (Perkin-Elmer R-32, 90 MHz) spectra of the enol acetates **2** were compared to the literature values.

Table. 2-Nitrocycloalkanones **3a-m** from Enol Acetates **2a-m** and Trifluoroacetyl Nitrate (**1**)

Compound No.	R ¹	R ²	Yield ^a [%]	m.p. [°C] or b.p. [°C]/torr	Molecular formula ^b or Lit. m.p. or b.p. [°C]/torr	I.R. ν [cm ⁻¹] medium	$\nu_{C=O}$	ν_{NO_2}
3a	H	H	~100	38–40°	39.5–40.5° ⁶	Nujol	1735	1555
3b	CH ₃	H	~100	34–35°	35.5–36.5° ⁵ ; 88–90°/1.5° ⁵	film	1730	1546
3c	CH ₃	6-CH ₃	85	71–73°/1.1	24–24.5° ⁵ ; 83–88°/1.9° ⁵	film	1729	1545
3d	CH ₃	4- <i>i</i> -C ₄ H ₉	~100	83–84°	83–84° ⁴	Nujol	1730	1535
3e	C ₂ H ₅	H	81	81°/0.9	C ₈ H ₁₃ NO ₃ (171.2)	film	1727	1542
3f	<i>n</i> -C ₃ H ₇	H	84	95–100°/0.9	C ₉ H ₁₅ NO ₃ (185.2)	film	1729	1545
3g	<i>n</i> -C ₄ H ₉	H	41	125–127°/2.1	C ₁₀ H ₁₇ NO ₃ (199.2)	film	1730	1542
3h	<i>i</i> -C ₃ H ₇	5-CH ₃	0	—	—	—	—	—
3i	<i>t</i> -C ₄ H ₉	H	18 ^c	78–79°	C ₁₀ H ₁₇ NO ₃ (199.2)	Nujol	1725	1540
3j	H	4- <i>i</i> -C ₄ H ₉	97 ^d	87–89°	87–90° ⁴	CHCl ₃	1739	1561
3k	H	3,3,5,5-tetra-CH ₃	95	76–77°	76–77° ⁴	CHCl ₃	1739	1558
3l	—	—	~100	76.5–77.5°	77–78° ³	Nujol	1730	1550
3m	—	—	~100	57–60°	C ₁₀ H ₁₅ NO ₃ (197.2)	CHCl ₃	1725	1545
2e	C ₂ H ₅	H	—	62.5°/1.9	C ₁₀ H ₁₆ O ₂ (168.2)	film	1755	1698 (C=C)
2f	<i>n</i> -C ₃ H ₇	H	—	76.5°/2.4	C ₁₁ H ₁₈ O ₂ (182.3)	film	1755	1700 (C=C)
2g	<i>n</i> -C ₄ H ₉	H	—	82.5°/1.7	C ₁₂ H ₂₀ O ₂ (196.3)	film	1751	1698 (C=C)

^a Product before recrystallization or distillation, purity checked by I.R. and N.M.R.^b Satisfactory microanalyses obtained: C \pm 0.22, H \pm 0.48, N \pm 0.42; microanalyses carried out by Galbraith Laboratories, Knoxville, Tennessee.^c Substrate **2i**; contains 15% 6-*t*-butyl-1-acetoxycyclohexene which gives on nitration *cis*-6-*t*-butyl-2-nitrocyclohexanone; yield: 51%; m.p. 109.5–110 °C.

C ₁₀ H ₁₇ NO ₃	calc.	60.28	8.60	7.03
(199.2)	found	60.21	8.74	6.94

I.R. (Nujol): ν = 1715 (C=O); 1549 cm⁻¹ (NO₂).¹H-N.M.R. (CDCl₃): δ = 1.00 (s, 9H); 5.25 ppm (dd, 1H, *J* = 9 Hz, 5 Hz).^d Kinetic mixture, 60:40, *cis/trans*, m.p. of *cis*-isomer given.**Nitration of Enol Acetates 2; General Procedure:**

In a 25-ml flask equipped with a condenser is placed the enol acetate **2** (3 mmol), preground ammonium nitrate (0.24 g, 3 mmol), and chloroform (3 ml). Trifluoroacetic anhydride (3 ml) is then added, and the mixture is stirred at room temperature for 1 h. The resulting solution is diluted with dichloromethane (25 ml), and poured into ice/water (25 ml). The aqueous layer is separated and extracted with dichloromethane (2 \times 20 ml). The combined organic layers are washed with cold 1% sodium hydrogen carbonate solution (25 ml), water (25 ml), saturated aqueous sodium chloride (25 ml), and dried with anhydrous magnesium sulfate. The solvent is evaporated to give the product **3** either as a viscous oil or a solid which is purified by either distillation or recrystallization.

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