A General Synthesis of 5,6-Dihydro-α-pyrones

R. W. Dugger and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

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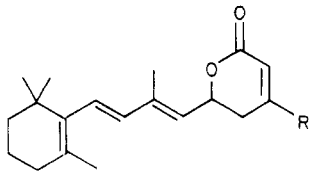
Crotonate esters substituted at C-3 by alkyl, alkoxy, or dialkylamino groups are deprotonated and the resulting dienolates added to aldehydes and ketones. Kinetic reaction is at C-2 of the ester, leading to the isolation of 2-alkyl-3-hydroxy esters such as **3** and **4** if the reaction mixture is quenched at −70 °C. However, retroaldolization occurs readily. If the initial reaction mixtures are allowed to warm to 15 °C before workup, the isolated products are 5,6-dihydro-α-pyrones (such as **5**), accompanied in some cases by the (*E*)-4-substituted crotonate (such as **6**). The method has been applied to the synthesis of a series of retinoid lactones (**5f**, **18**, **21a–c**) which are of interest as potential antineoplastic agents.

In connection with a project designed to prepare retinoic acid analogues for evaluation in the Sporn trachael organ culture,[1] we sought a general synthesis of lactones such as **1**. Although 5,6-dihydro-α-pyrones are fairly well-known



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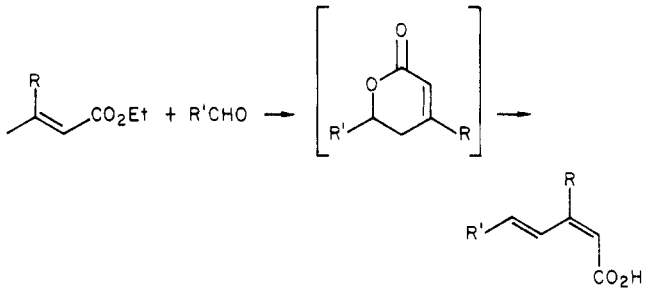
in nature,[2] there is no general route to this functionality. However, it is known that 3-substituted crotonate esters react with aldehydes under basic conditions to yield (*Z*,*E*)-dienoic acids, presumably by way of the corresponding lactones (Scheme I).[3] Consequently, we have examined the reaction of preformed enolates of 3-substituted crotonate esters with aldehydes and ketones.

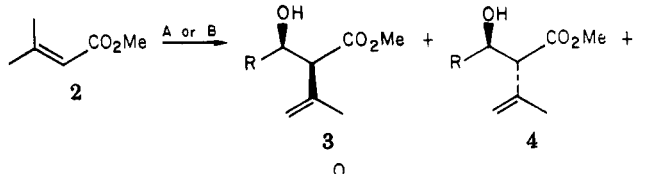
As a representative case, we first studied the reaction of methyl 3-methylcrotonate (**2**) with benzaldehyde. The ester is converted into its enolate by reaction with lithium diisopropylamide (LDA) in THF at −70 °C. Addition of benzaldehyde followed by quenching at −70 °C after 10 s affords a 60:40 mixture of β-hydroxy esters **3** and **4**.[4] However, if the reaction mixture is allowed to warm to 10–15 °C before being quenched, lactone **5** is obtained in 80% yield, along with 12% of the (*E*)-hydroxy ester **6**.

Results with other aldehydes and ketones are summarized in Scheme II and Table I. Several generalizations are possible. First, it is interesting that none of the other substrates studied give as high yields of lactone as does benzaldehyde. The two ketones studied (**13** and **14**) and the unsaturated aldehydes **10–12** all give modest yields of lactone (40–50%). However, isobutyraldehyde (**7**) gives lactone **5b** only in poor yield. Phenylacetaldehyde (**8**) and α-(benzyloxy)hexanal (**9**) both yield only the α adducts.

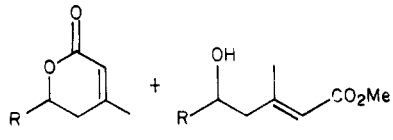
Scheme I



Scheme II[a]



2 **3** **4**



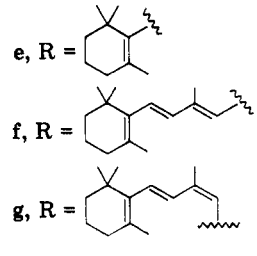
5 **6**

a, R = C_6H_5

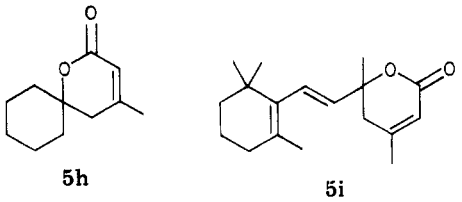
b, R = *i*-C_3H_7

c, R = $C_6H_5CH_2$

d, R = *n*-$C_4H_9CH(OCH_2C_6H_5)$



e, f, g



5h **5i**

[a] A: (1) LDA, THF, −70 °C; (2) RCHO, −70 °C; (3) NH_4Cl, H_2O, −70 °C. B: (1) LDA, THF, −70 °C; (2) RCHO, −70 °C; (3) warm to 10–15 °C; (4) NH_4Cl, H_2O.

We have also applied the lactone-forming reaction to methyl (*E*)-3-methoxybutenoate (**15**), which was condensed with benzaldehyde, isobutyraldehyde, cyclohexanone, and aldehyde **11**. Lactones **16–19** were produced in the indicated yields (Scheme III). With ester **15** hydroxy esters analogous to **6** are not isolated. However, isolated yields of lactones are comparable to those obtained by conden-

(1) M. B. Sporn, N. M. Dunlop, D. L. Newton, and W. R. Henderson, *Nature (London)*, **263**, 110 (1976).

(2) For example: Dioscorine: C. Page and A. Pinder, *J. Chem. Soc.*, 4811 (1964). Pestalotin: (a) G. Ellestad, W. McGahren, and M. Kunstmann, *J. Org. Chem.*, **37**, 2045 (1972). (b) Y. Kimura, K. Karagivi, and S. Tamura, *Tetrahedron Lett.*, 3137 (1971). Kava lactones: H. Achenbach and W. Regel, *Chem. Ber.*, **106**, 2648 (1973), and references therein.

(3) (a) E. E. Smissman and A. N. Voldeng, *J. Org. Chem.*, **29**, 3161 (1964); (b) M. Matsui, S. Okano, K. Yamashita, M. Miyano, S. Kitamura, A. Kobayashi, T. Sato, and R. Mikami, *J. Vitaminol.*, **4**, 178 (1958); (c) U. Schwieter, C. von Planta, R. Rüegg, and O. Isler, *Helv. Chim. Acta*, **45**, 528 (1962).

(4) The stereochemistry of these β-hydroxy esters was assigned by using the fact that for the carbinol proton $J_{threo} > J_{erythro}$: H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).

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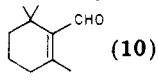
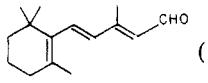
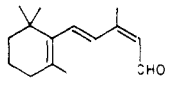
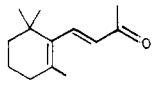
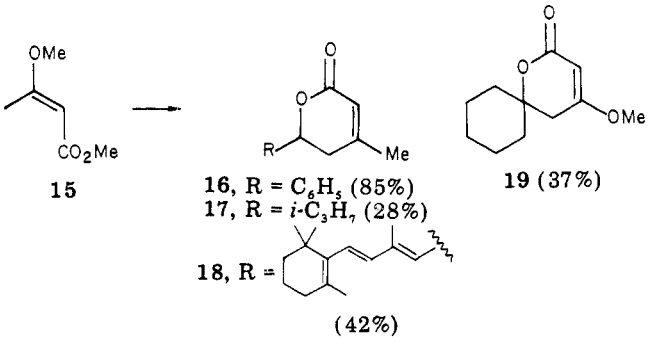
Table I. Condensation of Methyl 3-Methylbutenoate with Aldehydes and Ketones[a]

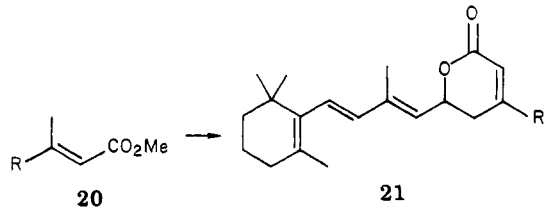
substrate	products, % yield 3	4	5	6
C_6H_5CHO	0	0	81	12
i-C_3H_7CHO (7)	3	12	20	7
$C_6H_5CH_2CHO$ (8)	--(54)--		0	0
$C_6H_5CH_2O$ | n-C_4H_9CHCHO (9)	--(100)--		0	0
 (10)	0	0	49	trace
 (11)	0	0	40	8
 (12)	0	0	44	0
 (13)	0	0	41	0
 (14)	0	0	42	0

[a] All reactions employed procedure B (Scheme II).

Scheme III



Scheme IV



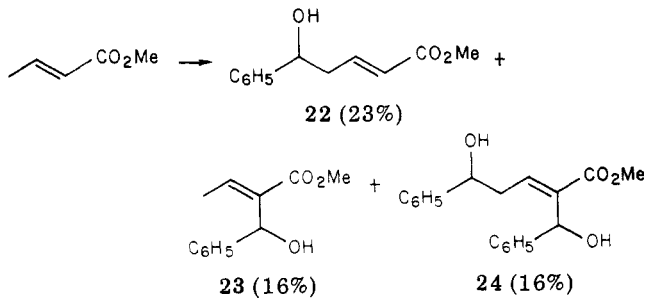
a, R = n-C_6H_{13} (14%); b, R = n-$C_5H_{11}O$ (19%); c, R = Me_2N (32%)

sation of a given substrate with ester **2**. Retinoid lactones **21a–c** were prepared by condensation of unsaturated esters **20a–c** with aldehyde **11** (Scheme IV). Although yields are low with these esters, the pure lactones are easily isolated by chromatography.

Dihydro-α-pyrones unsubstituted at the 4-position may not be obtained by this method. Methyl crotonate reacts with benzaldehyde to afford only hydroxy esters **22–24** (Scheme V).

A brief discussion of possible mechanism is in order. The results are consistent with the formulation in Scheme VI. The initial dienolate presumably exists as an equilibrium mixture of s-trans and s-cis conformers. The point of highest reactivity is at the α carbon and therefore the kinetic products resulting from short reaction times at low temperature are β-hydroxy esters such as **3** and **4**. However, retroaldolization is apparently rapid.[4,5] With longer reaction times, the thermodynamically more stable products from reaction at the γ position of the dienolate are produced. The s-trans conformer of the dienolate leads to the (E)-hydroxy ester, which cannot lactonize for geometric reasons. Reaction at the γ position of the s-cis conformer leads to the (Z)-hydroxy ester, which spontaneously lactonizes. With methyl crotonate itself, the absence of a 3-substituent causes the dienolate equilibrium to favor the s-trans form; thus, only the (E)-hydroxy ester and products derived from it are formed.

Scheme V



Scheme VI

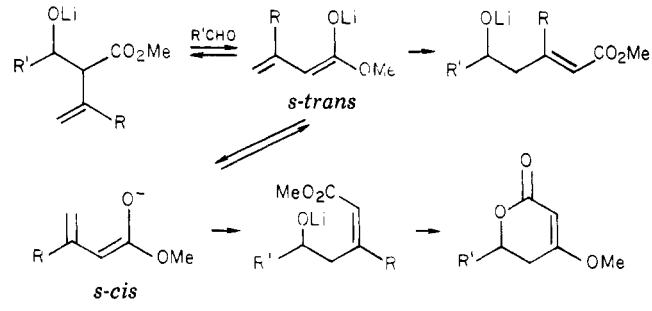


Table II. Activity of Retinoids in Tracheal Organ Culture[a]

compd	10^{-8} M	10^{-9} M
retinoic acid	236/236[b]	419/474[b]
5f	5/6	1/7
18	2/15	7/22
21a	1/7	
21b	1/6	1/7
21c	0/7	2/7

[a] Results are expressed in terms of the fraction of cultures in which the compound effectively reversed keratinization under defined in vitro conditions (see ref 1). [b] Data of D. L. Newton, W. R. Henderson, and M. B. Sporn, private communication.

Compounds **5f**, **18**, **21a**, **21b**, and **21c** were assayed in the Sporn tracheal organ culture.[1] Results are summarized in Table II, along with comparison data for retinoic acid. None of the lactones showed promising activity.

Experimental Section

All melting points (Pyrex capillary) are uncorrected. IR spectra were determined with a Perkin-Elmer Model 297 infrared recording spectrophotometer. ^1H NMR spectra were determined at 60 MHz with a Varian Model T-60 spectrometer or at 90 MHz with a Varian EM-390 spectrometer. The chemical shift values are expressed in δ values relative to internal tetramethylsilane. Significant ^1H NMR data are tabulated in parentheses in the order: number of protons, multiplicity, coupling constant(s) in

(5) The reversibility of the aldol reaction has been well established: (a) D. M. von Schriltz, E. M. Kaiser, and C. H. Hauser, *J. Org. Chem.*, 32, 2610 (1967); (b) Y. K. Lee and A. G. Schultz, *J. Org. Chem.*, 41, 4044 (1976).

hertz. ^{13}C NMR spectra were determined at 25.14 MHz on a Nicolet TT-23 spectrometer. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. All NMR spectra were taken in $CDCl_3$ unless otherwise noted. Ultraviolet spectra were recorded on a Cary Model 118 spectrophotometer; results are expressed as λ_{max} in nm (log ϵ). Preparative high-pressure liquid chromatography was conducted on a Waters Prep LC/System 500 with silica gel columns. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley.

Methyl 2-(Phenylhydroxymethyl)-3-methyl-3-butenoate (3 and 4). To a −70 °C solution of LDA (5.5 mmol) in 10 mL of THF was added 0.57 g (5 mmol) of ester **2** dropwise over a 15-min period. After the solution was stirred at −70 °C for 15 min, 0.53 g (5 mmol) of benzaldehyde was added all at once. Approximately 10 s later, the reaction was quenched by the addition of 10 mL of saturated aqueous NH_4Cl. The reaction mixture was diluted with water (20 mL) and extracted with ether (2 × 20 mL). The combined ether extracts were washed with water and brine (20 mL each) and dried over $MgSO_4$ and solvents were evaporated under reduced pressure to yield 1.01 g of a 60:40 mixture of **3** and **4** as a pale yellow oil. Analytical samples were obtained by chromatography on silica gel (3:2 hexane/ether).

High R_f diastereomer (possibly **3**):[4] IR (neat) 3450, 1730, 1645, and 805 cm^{-1}; ^1H NMR ($CDCl_3$ and D_2O) δ 1.78 (3 H, d, J = 1), 3.4 (1 H, m), 3.45 (3 H, s), 4.95–5.20 (3 H, m), and 7.25 (5 H, s). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 71.09; H, 7.21.

Low R_f diastereomer (possibly **4**):[4] IR (neat) 3450, 1730, 1645, and 805 cm^{-1}; ^1H NMR ($CDCl_3$ and D_2O) δ 1.50 (3 H, d, J = 1), 3.44 (1 H, d, J = 9), 3.70 (3 H, s), 4.75 (2 H, m), 5.03 (1 H, d, J = 9), and 7.23 (5 H, s). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.76; H, 7.34.

A General Procedure for the Synthesis of 5,6-Dihydro-α-pyrones. Dihydro-α-pyrone 18. Ester **15** (8.58 g, 66 mmol) was added dropwise to a −70 °C solution of LDA (73 mmol) in 130 mL of THF. After the solution was stirred for 20 min at −70 °C, β-ionylideneacetaldehyde (14.36 g, 66 mmol) in 20 mL of THF was added all at once. The reaction mixture was stirred for 5 min, the cooling bath was removed, and the reaction was allowed to warm to 10 °C (~25 min) and then quenched by the addition of 50 mL of saturated aqueous NH_4Cl. After dilution with water (200 mL), the mixture was extracted with ether (2 × 200 mL) and the combined ether layers were washed with water (2 × 100 mL) and brine (200 mL). Drying with $MgSO_4$ and evaporation of solvents at reduced pressure afforded 22.6 g of a viscous yellow oil. The crude product was dissolved in 60 mL of hot 4:1 hexane/ether and cooled to −15 °C overnight. Suction filtration and washing with ice-cold hexane yielded 8.72 g of pale yellow platelets (42%): mp 93.5–95 °C; IR (CCl_4) 1720, 1630, and 1215 cm^{-1}; ^1H NMR δ 1.00 (6 H, s), 1.67 (3 H, s), 1.87 (3 H, s), 2.3–2.6 (2 H, m), 3.73 (3 H, s), 4.95–5.55 (3 H, m), 5.86 (1 H, d, J = 16), and 6.20 (1 H, d, J = 16); ^{13}C NMR δ 13.0, 19.3, 21.6, 28.9, 32.9, 33.5, 34.2, 39.6, 56.0, 72.8, 90.6, 125.7, 128.8, 129.6, 136.2, 137.4, 139.5, 167.0, and 172.6; UV (MeOH) 233 (4.34), 268 (sh) (~4.08). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.77; H, 8.82.

4-Methyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-one (5) and Methyl 5-Hydroxy-3-methyl-5-phenyl-2-pentenoate (6). Reaction of benzaldehyde (2 mmol) and **2** yielded 0.399 g of a pale yellow oil. Chromatography on silica gel gave 0.306 g of **5** (81%) and 0.053 g of **6** (12%) as clear colorless oils.

5: IR (neat) 1710, 1645 cm^{-1}; ^1H NMR δ 1.92 (3 H, s), 2.3–2.6 (2 H, m), 5.26 (1 H, dd, J = 6, 10), 5.76 (1 H, m), 7.25 (5 H, s); ^{13}C NMR δ 22.7, 36.6, 78.6, 116.5, 126.0, 127.5, 128.5, 138.8, 156.7, and 164.3. After several days this oil crystallized, mp 60–61 °C (lit.[6] mp 61–62 °C).

6: IR (neat) 3500, 1710, 1640, 1600 cm^{-1}; ^1H NMR[7] δ 2.12 (3 H, d, J = 1), 2.45 (2 H, d, J = 7), 3.56 (3 H, s), 4.74 (1 H, t, J = 7), 5.61 (1 H, m), 7.25 (5 H, s); ^{13}C NMR δ 19.1, 50.5, 50.8, 72.2, 118.0, 125.8, 127.7, 128.5, 144.2, 155.9, and 166.5.

Reaction of 2 with Isobutyraldehyde. Reaction of isobutyraldehyde (10 mmol) with the enolate of **2** gave four products which were separated by preparative high-pressure LC (3:2 hexane/ether). The products in order of elution were as follows.

Methyl (3*RS*)-hydroxy-4-methyl-(2*SR*)-isopropenylpentanoate (4b) (3%), clear, colorless oil: IR (neat) 3525, 1735, and 1642 cm^{-1}; ^1H NMR δ 0.80–1.00 (6 H, m), 1.83 (3 H, d, J = 1), 3.20 (1 H, d, J = 8), 3.72 (3 H, s), 3.84 (1 H, m), and 5.00 (2 H, m). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.61; H, 9.62.

Methyl (3*SR*)-hydroxy-4-methyl-(2*SR*)-isopropenylpentanoate (3b) (12%), small white needles, recrystallized from hexane: mp 83–4 °C; IR (CCl_4) 3600, 3550, 1720, 1640 cm^{-1}; ^1H NMR δ 0.80–1.10 (6 H, m), 1.77 (3 H, d, J = 1), 3.24 (1 H, d, J = 9), 3.74 (3 H, s), 3.80 (1 H, m), and 4.93 (2 H, m). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.88; H, 9.60.

Methyl 3,6-dimethyl-5-hydroxy-2-heptenoate (6b) (7%), clear colorless oil: IR (neat) 3450, 1720, 1640 cm^{-1}; ^1H NMR δ 0.70–1.10 (6 H, m), 2.20 (3 H, d, J = 2), 2.2–2.6 (2 H, m), 3.60 (1 H, m), 3.70 (3 H, s), and 5.76 (1 H, m). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.41; H, 9.62.

5,6-Dihydro-6-isopropyl-4-methyl-2*H*-pyran-2-one (5b) (20%), clear colorless liquid: IR (neat) 1720, 1645, and 1250 cm^{-1}; ^1H NMR δ 0.80–1.10 (6 H, m), 2.20 (3 H, s), 2.1–2.4 (2 H, m), 4.10 (1 H, dt, J = 6, 9), and 5.70 (1 H, m). Anal. Calcd for $C_9H_{14}O_2$: C, 70.14; H, 9.09. Found: C, 70.23; H, 9.25.

4-Methyl-1-oxaspiro[5.5]undec-3-en-2-one (5h). Reaction of **2** with cyclohexanone on a 10-mmol scale furnished **5h** (41%) as a clear colorless oil after purification by preparative high-pressure LC (3:2 hexane/ether): IR (neat) 1705, 1650, and 1240 cm^{-1}; ^1H NMR δ 1.0–2.0 (10 H, m), 1.98 (3 H, d, J = 1), 2.34 (2 H, m), and 5.69 (1 H, m). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.01; H, 8.91.

Methyl 3-Hydroxy-2-isopropenyl-4-phenylbutyrate (3c and 4c). Reaction of phenylacetaldehyde (5 mmol) with **2** under the standard conditions afforded only recovered starting material and the α-aldol adducts **3c** and **4c** (54%) after chromatography on silica gel (3:1 hexane/ether). There was a trace of an impurity present which could not be separated from the hydroxy esters; IR (neat) 3500, 1730, 1641, 1601, and 900 cm^{-1}; ^1H NMR δ 1.77 (3 H, d, J = 1), 2.66 (2 H, dd, J = 3, 9), 3.10 (1 H, d, J = 9), 3.54 (3 H, s), 4.12 (1 H, dt, J = 3, 9), 4.92 (2 H, m), and 7.15 (5 H, s). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.17; H, 7.71.

Methyl 4-(Benzyloxy)-3-hydroxy-2-(1-methoxyvinyl)octanoate (3d, 4d). Reaction of **15** (5 mmol) with 2-(benzyloxy)-hexanal (**9**)[8] under the standard conditions afforded an inseparable mixture of **3d** and **4d** (and possibly their C-4 diastereomers) in quantitative crude yield: IR (neat) 3500, 1740, 1630, 1455, 1280, 1070 cm^{-1}; ^1H NMR indicated a mixture of products: δ 0.8–1.0 (methyl group, complex multiplet), 3.4–3.6 (several methoxy singlets), 4.0–4.5 (vinyl and carbinol protons, complex multiplet), 4.5–4.8 (benzylic protons, complex multiplet), and 7.31 (phenyl protons, singlet). An analytical sample was prepared by chromatography on silica gel (1:1 hexane/ether). Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.27; H, 8.48.

5,6-Dihydro-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2*H*-pyran-2-one (5e). β-Cyclocitral and **2** (5-mmol scale) yielded **5e** (49%) as a powdery white solid [mp 64–5 °C (lit.[9] mp 65–6 °C)] after purification by preparative high-pressure LC (7:3, hexane/ether): IR (CCl_4) 1720, 1645 cm^{-1}; ^1H NMR δ 1.00 (3 H, s), 1.13 (3 H, s), 1.79 (3 H, d, J = 1), 2.02 (3 H, s), 2.14 (1 H, dd, J = 4, 18), 2.84 (1 H, ddd, J = 0.5, 13, 18), 4.97 (1 H, dd, J = 4, 13), and 5.78 (1 H, m).

5,6-Dihydro-4,6-dimethyl-6-[2-(2,6,6-trimethyl-1-cyclohexen-1-yl)-(*E*)-ethenyl]-2*H*-pyran-2-one (5i). A 5-mmol scale reaction of β-ionone (**14**) with **2** yielded **13** (42%) as a clear colorless oil after preparative high-pressure LC (3:2 hexane/ether): IR (neat) 1715, 1645, 1240 cm^{-1}; ^1H NMR δ 0.95 (6 H, s), 1.55 (3 H, s), 1.60 (3 H, s), 1.95 (3 H, s), 2.99 (2 H, m), 5.38 (1 H, d, J = 16), 5.83 (1 H, m), and 6.04 (1 H, d, J = 16). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.64; H, 9.47.

(13*Z*)-11,12-Dihydro-11-hydroxyretinoic Acid δ-Lactone (5f) and Methyl 11,12-Dihydro-11-hydroxyretinoate (6f). Reaction of β-ionylideneacetaldehyde and **2** (3 mmol) under the

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standard conditions gave **5f** and **6f** after purification by preparative high-pressure LC (3:2 hexane/ether). Lactone **5f** (42%) crystallized upon standing [mp 67–8 °C (lit.[10] oil)] and **15** (8%) was an oil.

5f: IR (CCl_4) 1725, 1645, and 1240 cm^{-1}; ^1H NMR[10a] δ 1.02 (6 H, s), 1.68 (3 H, s), 1.90 (3 H, s), 1.98 (3 H, br s), 2.35 (2 H, m), 5.0–5.6 (2 H, m), 5.77 (1 H, m), 5.92 (1 H, d, J = 16), and 6.24 (1 H, d, J = 16); ^{13}C NMR δ 12.9, 19.3, 21.6, 22.9, 28.9, 32.9, 34.2, 35.1, 39.6, 74.2, 116.8, 125.9, 128.8, 129.6, 136.3, 137.4, 139.2, 156.9, 164.8; UV (MeOH) 225 (log ϵ 4.27) and 269 (log ϵ 4.08).

6f: IR (neat) 3640, 1705, 1640, and 1150 cm^{-1}; ^1H NMR δ 1.00 (6 H, s), 1.67 (3 H, s), 1.85 (3 H, d, J = 1), 2.28 (3 H, d, J = 2), 2.39 (2 H, m), 3.64 (3 H, s), 4.20 (1 H, m), 5.36 (1 H, br d, J = 8), 5.74 (1 H, m), 5.93 (1 H, d, J = 17), and 6.08 (1 H, d, J = 17). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.66; H, 9.95.

(9*Z*,13*Z*)-11,12-Dihydro-11-hydroxyretinoic Acid δ-Lactone (5g). Reaction of **2** and (*Z*,*E*)-β-ionylideneacetaldehyde (1 mmol) yielded **16** (44%) as a pale yellow oil after chromatography on silica gel (1:1 hexane/ether): IR (neat) 1720, 1640, 1240 cm^{-1}; ^1H NMR δ 1.02 (6 H, s), 1.68 (3 H, s), 1.93 (3 H, s), 1.97 (3 H, br s), 2.23 (2 H, m), 5.0–5.5 (2 H, m), 5.76 (1 H, m), and 6.23 (2 H, m); ^{13}C NMR 19.2, 20.4, 21.7, 22.9, 28.9, 32.9, 34.2, 35.6, 39.5, 73.4, 116.8, 124.6, 129.0, 129.9, 131.0, 137.8, 139.5, 156.8, and 164.8. Several attempts to obtain a correct combustion analysis failed. This lactone could be readily converted to the known (9*Z*,13*Z*)-retinoic acid by treatment with *t*-BuOK in THF at 0 °C, mp 133.5–134.5 °C (recrystallized from petroleum ether) (lit.[11] mp 135–136 °C).

5,6-Dihydro-4-methoxy-6-phenyl-2*H*-pyran-2-one (16). Benzaldehyde and **15** (5 mmol) under the standard conditions yielded **16** (85%) as a powdery white solid after recrystallization from benzene: mp 144–5 °C (lit.[12] mp 147–8 °C); IR (CCl_4) 1700, 1620, 1600 (sh), and 1380 cm^{-1}; ^1H NMR δ 2.4–3.0 (2 H, m), 3.74 (3 H, s), 5.20 (1 H, d, J = 1), 5.38 (1 H, dd, J = 5, 10), and 7.35 (5 H, s).

5,6-Dihydro-4-methoxy-6-isopropyl-2*H*-pyran-2-one (17).[13] Reaction of isobutyraldehyde (**7**) and **15** (5-mmol scale) gave **17** (28%) after chromatography on silica gel (1:1 hexane/ether): IR (neat) 1700, 1620 cm^{-1}; ^1H NMR δ 0.9–1.2 (6 H, m), 2.05 (1 H, m), 2.40 (2 H, m), 3.74 (3 H, s), 4.18 (1 H, m), and 5.17 (1 H, d, J = 1).

4-Methoxy-2-oxaspiro[5.5]undec-3-en-2-one (19). Cyclohexanone (**13**) and **15** (5-mmol scale) gave **19** (37%) after recrystallization from hexane: mp 80–1 °C; IR (CCl_4) 1700, 1630 cm^{-1}; ^1H NMR δ 1.2–2.1 (10 H, m), 2.42 (2 H, s), 3.69 (3 H, s), and 5.08 (1 H, s).

Reaction of Methyl Crotonate with Benzaldehyde (22–24). Treatment of the enolate of methyl crotonate with benzaldehyde under the standard conditions afforded three products which were separated by chromatography on silica gel (3:1 hexane/ether). The products in order of elution were (all were colorless oils) as follows.

(*E*)-Methyl 2-(phenylhydroxymethyl)-2-butenoate (22) (16%): IR (neat) 3500, 1700, 1640, and 1600 cm^{-1}; ^1H NMR δ 1.93 (3 H, d, J = 7), 3.60 (3 H, s), 5.74 (1 H, s), 7.10 (1 H, q, J = 7), and 7.35 (5 H, s). Anal. Calcd for $C_{11}H_{12}O_3$: C, 69.88; H, 6.84. Found: C, 70.05; H, 6.79.

(*E*)-Methyl 5-hydroxy-5-phenyl-2-pentenoate (23) (23%): IR (neat) 3500, 1705, 1640, and 1600 cm^{-1}; ^1H NMR[14] δ 2.56 (2 H, m), 3.52 (3 H, s), 4.70 (1 H, t, J = 7), 5.79 (1 H, dt, J = 1, 16), 6.91 (1 H, dt, J = 7, 16), and 7.27 (5 H, s).

(*E*)-Methyl 5-hydroxy-5-phenyl-2-(phenylhydroxymethyl)-2-pentenoate (24) (16%), presumably a mixture of diastereomers: IR (neat) 3400, 1700, 1640, 1600, and 900 cm^{-1}; ^1H NMR δ 2.68 (2 H, t, J = 7), 3.55 (3 H, s), 4.71 (1 H, t, J = 7), 5.61 (1 H, s), 6.90 (1 H, t, J = 7), 7.15 (5 H, s), and 7.25 (5 H, s). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.83; H, 6.36.

(13*Z*)-11,12-Dihydro-13-hexyl-11-hydroxy-13-norretinoic Acid δ-Lactone (21a). Reaction of the enolate of **20a**[15] (5 mmol) with (*E*,*E*)-β-ionylideneacetaldehyde afforded **21a** (14%) after chromatography on silica gel (4:1 hexane/ether) as a powdery pale yellow solid: mp 43–4 °C; IR (CCl_4) 1720, 1640, 1240 cm^{-1}; ^1H NMR δ 1.00 (6 H, s), 1.67 (3 H, s), 1.85 (3 H, s), 2.1–2.4 (4 H, m), 5.20 (1 H, m), 5.43 (1 H, d, J = 7), 5.75 (1 H, m), 5.92 (1 H, d, J = 16), and 6.19 (1 H, d, J = 16); ^{13}C NMR δ 12.9, 14.0, 19.3, 21.6, 22.5, 26.4, 28.9, 31.5, 32.9, 33.9, 34.2, 36.7, 39.6, 74.2, 115.7, 126.2, 128.6, 129.4, 136.4, 137.5, 139.1, 160.8, and 165.0; UV (MeOH) 227 (log ϵ 4.38) and 263 (log ϵ 4.13). Anal. Calcd for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34. Found: C, 81.03; H, 10.17.

Methyl (*E*)-3-Pentyloxycrotonate (20b). Sodium hydride (100 mmol, 4.8 g of a 50% oil dispersion) was slurried in 200 mL of a 1:1 mixture of THF and *N*,*N*-dimethylformamide. Then 1-pentanol (100 mmol, 8.8 g) was added dropwise over a 1-h period, followed by butynoic acid (40 mmol, 3.36 g) as a solution in 20 mL of THF. The mixture was heated to 100 °C (bath temperature) for 2 h and then poured into 1 L of ice-cold water. After the mixture was washed with ether (2 × 100 mL) the aqueous layer was acidified with 10% HCl and extracted with ether (2 × 200 mL). These ether extracts were combined, washed with brine (200 mL) and dried over $MgSO_4$ and the solvents were evaporated under reduced pressure to yield 8.64 g of a pale brown solid. Recrystallization from hexane gave 4.30 g (62%) of long off-white needles: mp 71–4 °C; IR ($CHCl_3$) 1685, 1610, 1295 cm^{-1}; ^1H NMR δ 0.90 (3 H, t, J = 6), 2.29 (3 H, s), 3.74 (2 H, t, J = 6), 4.96 (1 H, s). This material was of sufficient purity to use in the next reaction. An analytical sample was prepared by recrystallization from hexane/ether (1:1): mp 73–4 °C. Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 63.12; H, 9.27. Treatment of this acid (20 mmol, 3.44 g) with diazomethane in ether yielded **20b** (82%), after filtration through silica gel, as a clear, colorless liquid: IR (neat) 1710, 1610, 1280, 1140, 1050 cm^{-1}; ^1H NMR δ 0.90 (3 H, t, J = 6), 2.27 (3 H, s), 3.61 (3 H, s), 3.69 (2 H, t, J = 6), and 4.94 (1 H, s). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.41; H, 9.72.

(13*Z*)-11,12-Dihydro-11-hydroxy-13-nor-13-pentyloxyretinoic Acid δ-Lactone (21b). Condensation of (*E*,*E*)-β-ionylideneacetaldehyde (5 mmol) with **20b** gave **21b** (19%) after chromatography on silica gel (3:2 hexane/ether) as a pale yellow solid: mp 59–60 °C; IR (CCl_4) 1715, 1625, 1360, 1200 cm^{-1}; ^1H NMR δ 1.00 (6 H, s), 1.67 (3 H, s), 1.88 (3 H, s), 2.4–2.6 (2 H, m), 3.84 (2 H, t, J = 6), 5.07 (1 H, s), 5.20 (1 H, m), 5.43 (1 H, d, J = 8), 5.92 (1 H, d, J = 16), and 6.17 (1 H, d, J = 16); ^{13}C NMR δ 12.9, 13.9, 19.3, 21.5, 22.3, 28.0, 28.1, 28.9, 32.9, 33.6, 34.2, 39.6, 69.1, 72.7, 90.8, 107.5, 125.9, 128.7, 129.4, 136.3, 137.4, 139.4, 161.1, and 171.8; UV (MeOH) 236 (4.51) and 270 (sh) (~4.20). An analytical sample was prepared by recrystallization from hexane, mp 60–61 °C. Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37, H, 9.74. Found: C, 77.28; H, 9.84.

(13*Z*)-11,12-Dihydro-13-dimethylamino-11-hydroxy-13-norretinoic Acid δ-Lactone (21c). Reaction of **20c** with (*E*,*E*)-β-ionylideneacetaldehyde yielded **21c** (32%) as a pale yellow powder by crystallization from the crude reaction mixture (1:1 hexane/ether): mp 145–7 °C dec; IR (CCl_4) 1665, 1580, 1360 cm^{-1}; ^1H NMR δ 1.00 (6 H, s), 1.67 (3 H, s), 1.87 (3 H, s), 2.4 (2 H, m), 2.94 (6 H, s), 4.65 (1 H, s), 5.08 (1 H, dt, J = 9, 10), 5.48 (1 H, d, J = 9), 5.92 (1 H, d, J = 16), and 6.09 (1 H, d, J = 16); ^{13}C NMR δ 13.0, 19.2, 21.6, 28.9, 31.6, 32.9, 34.2, 39.2, 39.6, 71.9, 83.6, 107.5, 126.7, 128.3, 129.3, 136.4, 137.5, 138.6, 160.5, and 168.2; UV (MeOH) 282 (4.66). Anal. Calcd for $C_{21}H_{29}NO_2$: C, 76.55; N, 4.25; H, 9.48. Found: C, 76.42; N, 4.23; H, 9.31.

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Registry No. **2**, 924-50-5; **3a**, 72853-30-6; **3b**, 72853-31-7; **3c**, 72853-32-8; **3d**, 72853-33-9; **4a**, 72853-34-0; **4b**, 72853-35-1; **4c**, 72853-36-2; **5a**, 29643-79-6; **5b**, 65263-81-2; **5e**, 14393-37-4; **5f**,

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43059-50-3; **5g**, 72903-62-9; **5h**, 72853-37-3; **5i**, 72853-38-4; **6a**, 39652-50-1; **6b**, 72853-39-5; **6f**, 72903-63-0; **7**, 78-84-2; **8**, 122-78-1; **9**, 70326-39-5; **10**, 432-25-7; **11**, 3917-41-7; **12**, 54226-17-4; **13**, 108-94-1; **14**, 79-77-6; **15**, 35217-21-1; **16**, 17298-18-9; **17**, 55848-91-4; **18**, 72853-40-8; **19**, 1658-21-5; **20a**, 30801-80-0; **20b**, 72853-41-9; **20b** acid, 72853-42-0; **20c**, 72853-43-1; **21a**, 72853-44-2; **21b**, 72853-45-3; **21c**, 72853-46-4; **22**, 72853-47-5; **23**, 72853-48-6; **24**, 72853-49-7; benzaldehyde, 100-52-7; methyl crotonate, 623-43-8.

Nitroethylene: A Stable, Clean, and Reactive Agent for Organic Synthesis

Darshan Ranganathan,* C. Bhushan Rao, Subramania Ranganathan, Ashok K. Mehrotra, and Radha Iyengar

Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

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Contrary to current belief, nitroethylene is a stable reagent and holds promise as a useful and reactive synthon. Nitroethylene can be prepared in 20–25-g lots, and standard, refrigerated solutions in common solvents provide a good and ready source of the reagent. The reagent purity can be easily monitored by titration against tetraphenylcyclopentadienone (tetracyclone) coupled with the isolation of the colorless crystalline adduct. With reactive substrates, nitroethylene reacts with greatest ease at low temperatures, leading to functionalized systems having potential for further elaboration. With systems that require heating, the limited stability of nitroethylene itself complicates the course of the reaction. Cyclopentadiene, 5-[(benzyloxy)methyl]cyclopentadiene, 5-(methoxymethyl)cyclopentadiene, 5-(1,3-dithianyl)cyclopentadiene, 5-(trimethylsilyl)cyclopentadiene, and spiroheptadiene readily gave (4 + 2) adducts with nitroethylene, each possessing attraction as a synthetic intermediate. Adducts from furan and acetoxyfulvene undergo rearrangement via σ cleavage. The (4 + 2) adduct from 9-diazofluorene spontaneously extrudes nitrogen, leading to spironitrocyclopropane. Indole readily undergoes Michael addition to give 80% 3-(nitroethyl)indole and 15% of novel bis adduct. The 2,6 Michael adduct arises with 1-morpholinocyclohexene, and β-pinene undergoes an ene reaction with nitroethylene. Novel 2-nitroethyl phosphonates, useful in Wittig–Horner reactions, arise from nitroethylene and phosphites in *tert*-butyl alcohol.

Nitroethylene figures only in a few (4 + 2) reactions[1] and a handful of Michael additions.[2] Having become familiar with handling quantities of nitroethylene in connection with our efforts in the prostaglandin area,[3] we thought that it would be worthwhile to possibly project this reagent as a useful synthon with the aim of making it more popular and acceptable.

In sharp contrast to reports that highlight its instability,[4] we have found that nitroethylene is stable as a standard solution in benzene for at least 6 months when stored in a refrigerator (~10 °C). Additionally, the highly characteristic NMR of nitroethylene (vide infra) is not changed at all under the above conditions, and the yield of isolated adducts with standards such as cyclopentadiene and tetracyclone is hardly affected during this period of storage.

Thus, 20–25-g batches of nitroethylene have been prepared in one lot and stored as a 10% solution in benzene at ~10 °C. Of the several methods that are available for the preparation of nitroethylene, in our hands, the phthalic

Table I. ^{1}H NMR Data for Nitroethylene[a] Adducts with Cyclopentadienes[b,c]

adduct	^{1}H NMR data[d]
1	6.4, 5.9 (2 q, olefinic), 5.0 (m, $HCNO_2$), 3.5, 3.0 (both br, bridgehead)[e]
2	6.32, 5.9 (2 q, olefinic), 5.1 (m, $HCNO_2$), 3.55, 2.92 (both br, bridgehead), 3.3 (d, J = 8 Hz, OCH_2CH), 3.3 (OCH_3)[f]
2a	6.45 (q), 5.75 (d) (olefinic), 5.13 (q, $HCNO_2$), 3.9 (dd, OCH_2C), 3.46 (OCH_3), 3.0 (br, bridgehead)[e]
3	7.28 (aromatic), 6.23, 5.8 (2 q, olefinic), 4.9 (m, $HCNO_2$), 4.4 (OCH_2Ph), 3.3 (d, J = 7 Hz, OCH_2CH), 3.42, 2.9 (both br, bridgehead)[e]
3a	7.25 (aromatic), 6.32 (q), 5.7 (d) (olefinic), 5.1 (q, $HCNO_2$), 4.6 (OCH_2Ph), 3.9 (dd, OCH_2C), 2.9 (br, bridgehead)[e]
4	6.3, 5.85 (2 q, olefinic), 4.97 (m, $HCNO_2$), 4.0 (d, J = 10.5 Hz, -H(S_2), 3.76, 3.15 (both br, bridgehead), 2.75 (m, S-CH_2)[f]
5	6.35, 5.9 (2 q, olefinic), 5.0 (m, $HCNO_2$), 3.6, 3.1 (both br, bridgehead), O($SiMe_3$)[e]
6	6.4, 5.95 (2 q, olefinic), 5.01 (m, $HCNO_2$), 0.52 (m, cyclopropane protons)[e]

[a] Nitroethylene: ^{1}H NMR δ 6.55 (dd, J = 7 and 15 Hz, $=C(NO_2)H$), 5.85 (dd, J = 15 and 2 Hz, syn H), 5.22 (br d, J = 7 Hz, anti H). [b] The adducts **1–6** exhibited IR (neat/KBr) ν_{max} 1534 ± 5 and 1368 ± 2 cm^{-1} for the nitro function. [c] For **7**, the tetraphenylcyclopentadienone–nitroethylene adduct: IR (KBr) ν_{max} 1786 (strained C=O), 1550, 1361 (nitro). [d] In δ with Me_4Si as internal standard. [e] CCl_4. [f] $CDCl_3$.

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