Cyclopolymerization and Regioselective Synthesis of Vinyl Itaconates

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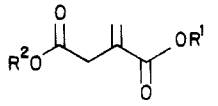
A selective synthesis for both 1- and 4-alkyl vinyl itaconate regioisomers is presented. Polymerization experiments with these two monomers reveal that only 4-vinyl itaconic acid (**3a**) and 1-alkyl 4-vinyl itaconates (e.g., **8**) lead to cyclopolymers. A synthesis of the γ-lactone repeating unit found in the cyclopolymer confirms the structure and stereochemistry of the polymer.

Recently, there has been growing synthetic interest in the use of free radical cyclizations to prepare five-membered rings. This approach has been utilized, for example, to construct small carbocycles such as alkaloids,[1,2] lactams,[3] and butenolides,[4] as well as larger molecules including polymers.[5] During our work with itaconic acid, **1**, we



1, R^1; R^2 = H
2a, R^1 = CH=CH_2; R^2 = H
b, R^1 = CH=CH_2; R^2 = CH_3
3a, R^1 = H; R^2 = CH=CH_2
b, R^1 = CH_3; R^2 = CH=CH_2
4, R^1 = CH=CH_3; R^2 = CH=CH_2

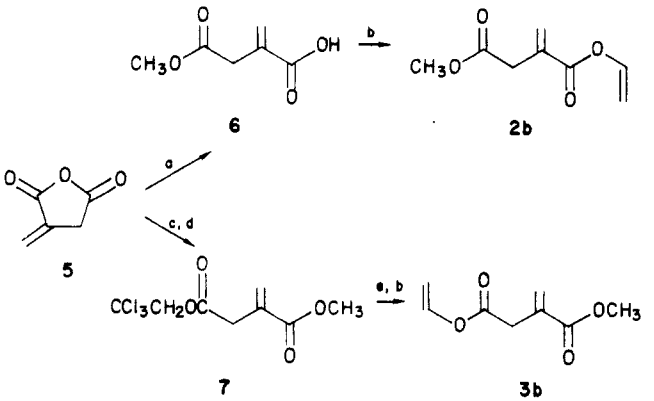
became intrigued with the possibility of preparing derivatives that might cyclopolymerize under free radical conditions to form polymeric lactones. It seemed possible that either of the two half acid half vinyl esters **2a** or **3a** (or the corresponding methyl vinyl esters **2b**, **3b**) might be suitable precursors.

In this paper we describe both a convenient synthesis for the 1-vinyl and 4-vinyl itaconates, **2** and **3**, respectively, and their subsequent reaction with free radical initiators. Itaconates **3** were found to cyclopolymerize and the ring size and stereochemistry were determined spectroscopically by comparison to model compounds. In contrast, 1-vinyl 4-methyl itaconate (**2b**) did not cyclopolymerize but afforded a cross-linked polymer.

Results and Discussion

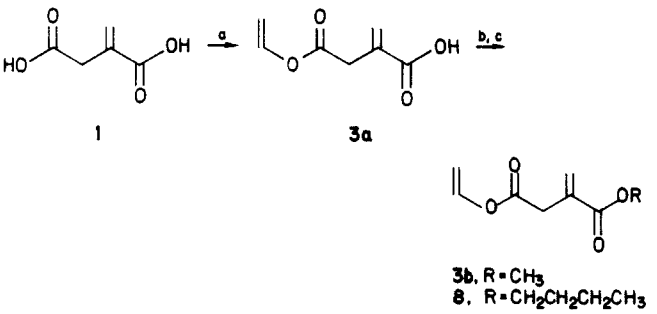
Synthesis. Itaconic anhydride (**5**) is known to react with alcohols regioselectively to afford 4-alkyl itaconates.[6] This selectivity allowed for the straightforward synthesis of 1-vinyl 4-methyl itaconate (**2b**) as illustrated in Scheme I. Reaction of itaconic anhydride with methanol gave 4-methyl itaconate (**6**), which under transesterification conditions in the presence of vinyl acetate led to **2b**. The other regioisomer was prepared by using a similar approach, Scheme I. In this instance, itaconic anhydride was selectively opened with trichloroethanol to form the half acid, half trichloroethyl ester followed by diazomethane to afford the diester **7**. The trichloroethyl functionality

Scheme I[a]



[a] (a) CH_3OH; (b) $LiCl_2$·$PdCl_2$, vinyl acetate; (c) CCl_3CH_2OH, BF_3·$2Et_2O$; (d) CH_2N_2; (e) Zn/HCl(aq) ethanol.

Scheme II[a]



[a] (a) $BF_3/Hg(OAc)_2$, vinyl acetate; (b) $SOCl_2$; (c) NEt_3, ROH.

Table I. Effect of Solvent Concentration and Reaction Time on Product Ratio of 3a to 4 during the Transvinylation of Itaconic Acid and Vinyl Acetate

reactn time, h	[dimethoxyethane], M	% reactn	3a/4
1	6.4	12	79
2.5	6.4	21	42
4	6.4	28	29
5	6.4	31	23
6	6.4	33	22
16	6.4	45	7.9
16	0	50	1
16	3.6	27	3.4
16	5.6	37	5.5
16	7.1	49	20

[a] Reactions were run at 25 °C.

was removed with zinc and hydrochloric acid and the resulting half acid ester was converted to 1-methyl 4-vinyl itaconate (**3b**) by transesterification with vinyl acetate.

Since the synthetic sequence leading to **3** was cumbersome on a large scale, an alternate one-step preparation was sought. It was found that 4-vinyl itaconate could be

(1) Ueno, Y.; Chino, K.; Watanabe, M.; Mariya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564.
(2) Hart, J. D.; Tsai, Y. M. *J. Am. Chem. Soc.* **1982**, *104*, 1430.
(3) Bachi, M. D.; Frolow, F.; Hoornaert, J. *J. Org. Chem.* **1983**, *48*, 1841.
(4) Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1983**, *105*, 3720.
(5) (a) Butler, G. B.; Kresta, J. E. *Cyclopolymerization and Polymers with Chain-Ring Structures*; ACS Symposium Series 195, American Chemical Society: Washington, DC, 1982. (b) Butler, G. B. *J. Macromol. Sci. Chem.* **1984**, *421*, 1547.
(6) Barker, B. R.; Schaub, R. E.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 116.

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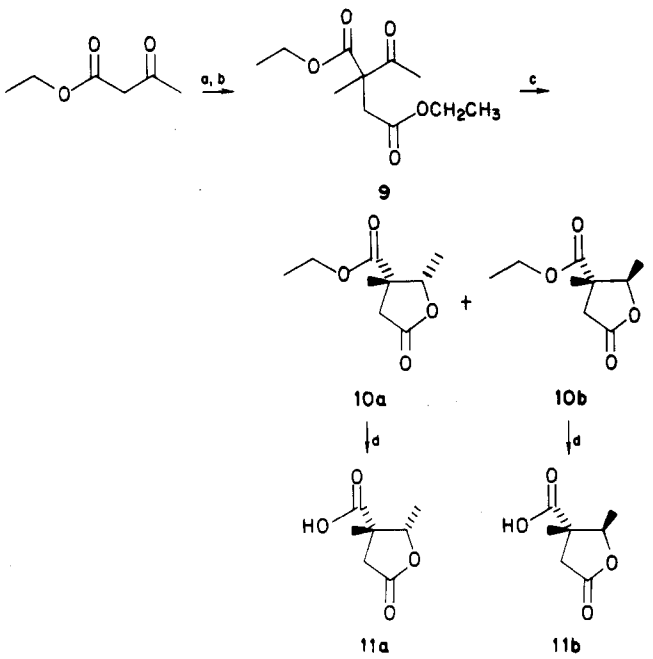
Scheme III[a]



[a] (a) Na, EtOH, CH_2BrCO_2Et; (b) Na, EtOH, CH_3I; (c) $NaBH_4$, EtOH; (d) $MeSO_3H$/aqueous HCO_2H.

conveniently synthesized by a mercury acetate/boron trifluoride catalyzed transesterification of itaconic acid and vinyl acetate, Scheme II. The major product of this reaction, if run neat, is divinyl itaconate (4). However, with tetrahydrofuran or dimethoxyethane as the solvent and limiting the conversion to 50%, a twentyfold excess of **3a** over 4 could be realized. Table I summarizes the effect of reaction time and solvent concentration on this ratio. The unreacted itaconic acid was easily removed due to its limited solubility in solvents like dichloromethane. Alkyl vinyl esters were prepared from **3a** by treatment with thionyl chloride followed by, for example, 1-butanol and triethylamine to yield the corresponding butyl ester 8 in good yield.[7]

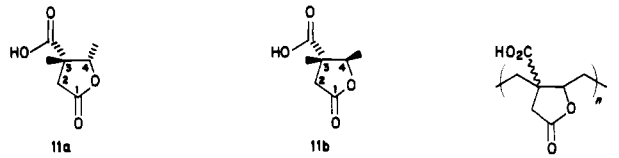
Polymerization. When 1-vinyl 4-methyl itaconate (**2b**) is heated in ethyl acetate with small amounts of azobis(isobutyronitrile) (AIBN), an insoluble gel is obtained at conversions greater than 20%. If the polymerization is quenched before gelation, the isolated polymer can be redissolved in THF. However, from the infrared spectrum there is no evidence for a polymeric lactone owing to the absence of bands above 1750 cm^{-1}. Also, it appears that mainly the acrylate double bond participates in the polymerization, based on ^{13}C NMR data.

In contrast, when either compound **3a** or 8 is subjected to free radical conditions, the reactions could be carried to higher conversions and the resulting polymers were soluble in tetrahydrofuran and acetonitrile. The infrared spectrum of the polymer from 8 had two carbonyl absorptions at 1730 and 1790 cm^{-1} compared with 1726 and 1757 cm^{-1} for the monomer. In addition, the absorption bands at 1640 and 1644 cm^{-1} for the two carbon–carbon double bonds almost completely disappeared in the polymer, indicating that both double bonds participate in the polymerization.

These results, especially the infrared band at 1790 cm^{-1}, suggest the formation of a polymeric γ-lactone. Two model

(7) The butyl rather than the methyl ester was routinely prepared owing to its greater ease of separation from small amounts of divinyl itaconate by distillation.

Table II. ^1H and ^{13}C NMR Chemical Shifts and Assignments for the Isomeric Lactones, 11a and 11b, and ^{13}C NMR Chemical Shifts for the Polymer Derived from 3a



chemical shift[a]		chemical shift[a]			chemical shift[b]	
^{13}C	^1H	^{13}C	^1H	assignment[c]	^{13}C	^{13}C
178.4		178.5		1	177.5	177.1
173.5		174.5		$CO_2H(3)$	174.5	175.6
82.2	4.43 (q)	80.2	4.83 (q)	4	87.0	85.7
49.3		48.9		3	54.6	53.6
39.4	3.09 (d), 2.44 (d)	40.4	3.17 (d), 2.50 (d)	2	36.6	38.1
20.3	1.46 (s)	17.2	1.35 (s)	$CH_3(3)$		
15.2	1.39 (d)	14.9	1.42 (d)	$CH_3(4)$		

[a] In $CDCl_3$. [b] In D_2O/HCO_2H. [c] Reference 10.

Table III. CS_2 Charge Exchange Mass Spectra of 11a and 11b

compd	ions (m/z) and relative intensities[a]
11a	159 (100), 142 (6), 114 (23), 99 (3), 86 (2)
11b	159 (100), 130 (5), 116 (36), 114 (7), 98 (7), 86 (3)

[a] The relative intensities are listed in parentheses.

compounds **11a** and **11b** were synthesized by the route shown in Scheme III to confirm this assignment. Ethyl acetoacetate was alkylated first with ethyl 2-bromoacetate and then with methyl iodide to yield **9** which when reduced with sodium borohydride gave a mixture of two diastereomeric lactones **10a** and **10b**. These were separated by liquid chromatography and then hydrolyzed to the corresponding acids **11a** and **11b** in aqueous formic acid. Although the ^1H and ^{13}C NMR chemical shifts were different for the diastereomers, stereochemical assignments were made on the basis of nuclear Overhauser effect (NOE) difference ^1H NMR[8] and low-energy charge exchange (CE) mass spectrometry.[9]

For the NOE experiment, the methyl singlet resonance due to the methyl protons on C3 (Table II) of either isomer was irradiated under identical conditions. For one isomer (**11a**) the intensity of the signal of the methine proton on C4 was enhanced significantly, whereas this enhancement was reduced for the other isomer. These results are interpreted in terms of the spatial proximity of the proton on C4 to the irradiated methyl protons. The enhancement occurs when the methyl and methine protons in question are on the same face of the ring. Consequently, the spectrum containing the enhancement can be assigned to the isomer having a trans configuration for the two methyl groups, **11a**.

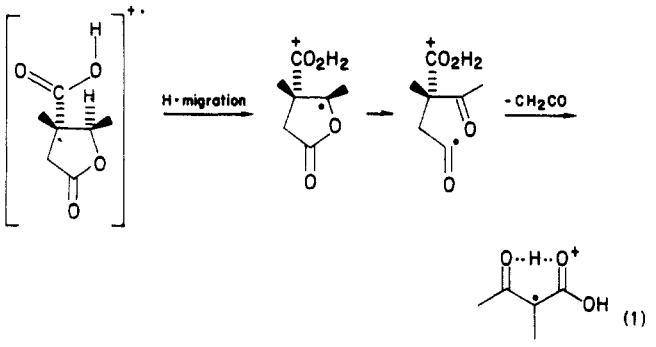
This stereochemical assignment was independently verified by low-energy CE mass spectrometry. Although the CS_2 CE mass spectra of both isomers exhibit an

(8) Sanders, J. K. M.; Mersh, J. D. *Prog. NMR Spectrosc.* **1983**, *15*, 353.

(9) (a) Li, Y. H.; Herman, J. A.; Harrison, A. G. *Can. J. Chem.* **1981**, *59*, 1983. (b) Harrison, A. G. *Chemical Ionization Mass Spectroscopy*, CRC Press: Boca Raton FL, 1983; pp 12–15. (c) Keough, T.; Mihelich, E. D.; Eickhoff, D. *Anal. Chem.* **1984**, *56*, 1849.

(10) The assignments in Table II are based on the the NOE difference spectral results and are consistent with previous NMR studies of substituted γ-butyrolactones, see: (a) Bystrom, S.; Hogberg, H. E.; Norin, T. *Tetrahedron* **1981**, *37*, 2249. (b) Kolsaber, P.; Stromberg, A. *Acta Chem. Scand., Ser. B* **1979**, *B33*, 755.

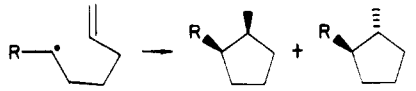
identical parent ion (MH^+) at m/z 159, there are significant differences in the fragmentation patterns (Table III). The major difference between the two isomers occurs at m/z 114, assigned as $(M - CO_2)^+$ and/or $(M - C_2H_4O)^+$, and at m/z 116, assigned as $(M - CH_2CO)^+$.[11] Whereas isomer **11b** has signals at both m/z 116 and 114 with relative intensities of 36 and 7, respectively, isomer **11a** has only a peak at 114 with a relative intensity of 23. This difference in fragmentation can be explained on the basis of stereochemistry. If isomer **11b** has the methyl groups in a cis configuration, it is properly oriented for an intramolecular hydrogen transfer via a cyclic transition state. Upon transfer of the methine hydrogen on C-4 to an oxygen atom of the acid, it will preferentially fragment by loss of ketene (eq 1) and afford a peak at m/z 116. Spa-



(1)

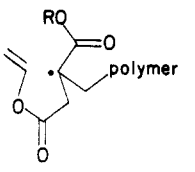
tially dependent hydrogen migrations, such as the one proposed, are well-known in mass spectrometry and have been previously used for stereochemical determinations.[12] The trans isomer, **11a**, lacks the favorable configuration for a hydrogen atom migration[13] and it fragments by elimination of carbon dioxide and/or acetaldehyde.

With the stereochemical assignment of the two model lactones complete, it was of interest to compare their ^{13}C NMR spectra to that of the polymer derived from **3a**. The data in Table II demonstrate how closely the spectra of **11a** and **11b** compare with that of the polymer from **3a**. Consequently, it can be concluded that cyclopolymerization of monomer **3a** has occurred and, judging from the relative peak heights, the polymer consists of nearly an equal mixture of the stereoisomeric γ-lactones. Earlier work on exo-1,5-ring closures of hexenyl radicals monosubstituted on C-1 does not predict a definitive stereochemical outcome, eq 2.



(2)

In cases where the C-1 substituent was small (R = CH_3, CH_2CH_3), the cis to trans ratio was 2.3.[14] However, this ratio dropped to 0.5 when the substituent was made more bulky (R = $CH_2C(CH_3)_2CO_2H$).[15] Perhaps it is not surprising that the 1,1-disubstituted alkenyl radical **12** in the present work showed no pronounced selectivity in the ring closure. Finally, from a consideration of Beckwith's rules



12

it follows that only monomer **3** will undergo a cyclopolymerization since ring closure can proceed through a favorable 5-exo-trig transition state.[16]

Experimental Section

Melting points were measured on a Thomas-Hoover capillary melting point apparatus and were uncorrected. IR spectra were obtained as neat films or from KBr pellets with a Perkin-Elmer Model 298 spectrometer. Low field ^1H NMR and ^{13}C NMR spectra were obtained on Varian EM-360 and Varian CFT-20 spectrometers, respectively, using Me_4Si as the internal standard. High field ^1H NMR and ^{13}C NMR spectra were obtained on a JEOL FX-270 spectrometer operating at 270 and 67.8 MHz, respectively. Chemical shifts are reported relative to external Me_4Si and samples for the high field work were dissolved in either D_2O/HCO_2H or $CDCl_3$. The CE mass spectra were obtained by direct injection into a Hewlett-Packard 5958B GC/MS system by using previously described procedures.[9c] Elemental analysis were performed by Galbraith Laboratories, Knoxville, TN. Thin-layer chromatography was carried out on 0.25-mm precoated silica gel plates from Analtech and visualized by charring with phosphomolybdic acid in ethanol. Flash chromatography and medium pressure chromatography were performed on silica gel 60 (E. Merck particle size 0.040–0.063 mm). Gas chromatography was run on a Varian 3700 on a 10 ft × $^1/_8$ in. column packed with equal amounts of 10% OV-17 on Chromsorb Q and 10% SE-30 on Chromsorb W.

1-Vinyl 4-Methyl Itaconate (2b). 4-Methyl itaconate (**6**)[6] (1100 g, 7.64 mol) was combined with 5.5 L of vinyl acetate (59.7 mol). To this mixture was added 0.05 mol of LiCl–$PdCl_2$ complex prepared by heating $PdCl_2$ (5.87 g, 0.05 mol) and LiCl (2.12 g, 0.05 mol) in methanol (25 mL) until the solution became homogeneous. The catalyst solution was concentrated in vacuo and the residue was taken up in vinyl acetate and concentrated again. The catalyst was added to the reaction mixture and the solution refluxed for 17 h. Since GC analysis revealed the reaction to be only 35% complete, an equivalent amount of fresh catalyst was added the reaction mixture refluxed for an additional 14 h. The reaction mixture was washed with water (6 × 1000 mL), followed by saturated $NaHCO_3$ (1000 mL), and brine (1000 mL). The organic phase was concentrated to about half volume, dried ($MgSO_4$), and passed through a pad of alumina. The Al_2O_3 was washed with ether and the ether washings were combined with the residue. The solution was concentrated in vacuo and distilled to afford 882 g (68%) of **2b** as a pale yellow liquid:[17] bp 63 °C (0.04 torr); IR 1735 (br), 1640, 1435, 1320, 1260, 1145, 945 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.22 (dd, 1 H), 6.37 (s, 1 H), 5.78 (m, 1 H), 4.55–5.04 (m, 2 H), 3.66 (s, 3 H), 3.35 (m, 2 H); ^{13}C NMR (20 MHz, $CDCl_3$) 170.8, 163.2, 141.3, 133.1, 130.1, 98.2, 52.0, 37.3. Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.23; H, 5.77.

1-Methyl 4-Vinyl Itaconate (3b). Itaconic anhydride (7.5 g, 0.067 mol), trichloroethanol (18.0 g, 0.120 mol), and boron trifluoride etherate (1 mL) were combined at room temperature and heated for 30 min at 95 °C with a constant stirring under argon. After being cooled to room temperature, the reaction solution was partioned between aqueous bicarbonate and ether. The aqueous bicarbonate was acidified with 4 M HCl and extracted with ether (3 × 100 mL). The etheral layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and rotoevaporated to leave 5.9 g (34%) of **7** as a pale yellow liquid which

(11) (a) Friedman, L.; Long, F. A. *J. Am. Chem. Soc.* **1953**, *75*, 2832. (b) McFadden, W. H.; Day, E. A.; Diamond, M. J. *Anal. Chem.* **1965**, *37*, 89. (c) Honkanen, E.; Moisio, T.; Karvonen, P. *Acta Chem. Scand.* **1965**, *19*, 370.

(12) Mandelbaum, A. *Mass Spectrom. Rev.* **1983**, *2*, 223 and references cited.

(13) Fenselau, C. C.; Robinson, C. H. *J. Am. Chem. Soc.* **1971**, *93*, 3070.

(14) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613.

(15) Bradney, M. A. M.; Forbes, A. D.; Wood, J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1655.

(16) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482.

(17) 1-Vinyl itaconic acid (**2a**) could be prepared from 1-vinyl 4-methyl itaconate (**2b**) by selective hydrolysis of the methyl ester using aqueous sulfuric acid.

was immediately esterified with diazomethane (prepared from *N*-nitroso-*N*-methylurea) to afford 1-methyl 4-trichloroethyl itaconate which after purification on a Waters Prep 500 (4:1 v/v hexane/ethyl acetate on silica gel) and distillation was obtained in 43% yield (2.75 g) as a colorless liquid: bp 104–106 °C (0.2 torr); IR (neat) 1760, 1725, 1635 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.35 (s, 1 H), 5.76 (m, 1 H), 4.74 (s, 2 H), 3.77 (s, 3 H), 3.49 (m, 2 H); ^{13}C NMR (20 MHz, $CDCl_3$) 168.8, 166.1, 133.2, 128.8, 95.0, 74.2, 52.0, 37.2. 1-Methyl 4-trichloroethyl itaconate was dissolved in 20% aqueous ethanol (30 mL) and concentrated HCl (1.5 mL) and cooled to 5 °C in an ice bath. Zinc dust (3.3 g, 50 mmol) was added with constant stirring in three portions over a 10-min interval. After being stirred an additional 20 min at 0 °C, the reaction was filtered to remove any unreacted zinc and insoluble zinc salts. The filtrate was added to water (50 mL) and extracted with ether (3 × 100 mL). The ether washings were combined, washed once with brine (100 mL), dried, ($MgSO_4$) and rotoevaporated to leave 1.35 g (94%) of **3a** as a colorless liquid, which was immediately converted to 1-methyl 4-vinyl itaconate (**3b**) with vinyl acetate and $PdCl_2$·LiCl by the identical method described for the conversion of **6** to **2b**: bp 58 °C (0.1 torr); IR 1765, 1725, 1645, 1442, 1325, 1145, 992, 590, 880, 820 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.17 (dd, 1 H), 6.29 (s, 1 H), 5.70 (m, 1 H), 4.46–5.02 (m, 2 H), 3.73 (s, 3 H), 3.37 (m, 2 H); ^{13}C NMR (20 MHz, $CDCl_3$) 167.8, 166.3, 141.2, 133.1, 129.0, 98.0, 52.2, 37.3. Anal. Calcd for $C_8H_{10}O_4$: C, 56,47; H, 5.92. Found: C, 56.30; H. 6.01.

4-Vinyl Itaconate (3a). Itaconic acid (40.0 g, 0.31 mol), vinyl acetate (27.0 g, 0.31 mol), mercuric acetate (1.7 g, 0.012 mol), and dry tetrahydrofuran (0.13 L) were mechanically stirred in a 500-mL, three-necked flask equipped with a drying tube. After 16 h at room temperature, ammonium sulfide (1 mL, 28% in water) and triethylamine (1.3 g, 0.013 mol) were added and this mixture was stirred for an additional hour. The resulting black solid was removed by filtration through Celite, and the filtrate was concentrated by rotoevaporation to leave a gray solid. This solid was added to methylene chloride (170 mL) and filtered. The filtrate was washed with water (3 × 20 mL), dried over $MgSO_4$, and rotoevaporated to leave 15 g of a golden liquid. This liquid was dissolved in *n*-butyl chloride followed by addition of hexane until cloudy. Upon cooling, 7.7 g (16% uncorrected) of **3a** was obtained as white crystals: mp 54–56 °C; IR (KBr) 1750, 1690, 1630, 982, 948, 937, 916, 880 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.18–7.5 (m, 1 H), 6.8 (m, 1 H), 5.95 (m, 1 H), 4.5–5.05 (m, 2 H), 3.42 (m, 2 H); ^{13}C NMR (20 MHz) δ 171.6, 167.8, 141.3, 132.7, 131.7, 98.4, 36.9. Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.89; H, 5.29.

1-*n*-Butyl 4-Vinyl Itaconate (8). 4-Vinyl itaconate (**3a**) (10.0 g, 0.064 mol) was dissolved in methylene chloride (100 mL) and stirred at reflux with DMF (5 drops) and thionyl chloride (10.0 g, 0.084 mol) under anhydrous conditions for 6 h. The volatiles were removed by evaporation and the residue was dissolved in diethyl ether (100 mL) containing 1-butanol (4.74 g, 0.064 mol). This solution was cooled in an ice bath under anhydrous conditions while triethylamine (6.47 g, 0.064 mol) was added dropwise. After 1 h, the white precipitate which had formed was removed by filtration and the supernate washed with 10% HCl (3 × 100 mL), saturated bicarbonate (3 × 100 mL), and water (3 × 100 mL). After drying ($MgSO_4$), the solution was concentrated by aspiration and distilled to give 8.6 g (63%) of **8**: bp 80–82 °C (0.1 torr); IR 2963, 1757, 1726, 1642, 1465, 1420, 1320, 1140, 992, 948, 876, 812 cm^{-1}; ^1H NMR δ 7.30 (dd, 1 H), 6.43 (s, 1 H), 5.83 (m, 1 H), 4.75 (m, 2 H), 4.14 (t, 2 H), 3.40 (m, 2 H), 2.08 (s, 2 H), 0.8–1.8 (m, 7 H); ^{13}C NMR 167.8, 165. 9, 141.3, 133.5, 128.8, 97.9, 65.0, 37.4, 30.6, 19.2, 13.7. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.18; H, 7.31.

Diethyl 2-Acetyl-2-methylsuccinate (9). Sodium metal (1.2 g, 0.052 mol) was added to absolute ethanol (40 mL) under positive argon pressure and the solution heated gently until all the sodium reacted. After the sequential dropwise addition of ethyl acetosuccinate[18] (10.8 g, 0.050 mol) and methyl iodide (7.1 g, 0.050 mol), the temperature was brought to 70 °C and maintained for 16 h. Upon cooling and partially removing solvent under aspirator pressure, the reaction was partitioned between a water (50 mL) and ether (100 mL). The ether layer was washed with 0.1 N HCl (50 mL) and brine (50 mL) and then dried ($MgSO_4$). Upon distillation 8.4 g (73%) of **9** was obtained as a colorless liquid: bp 125–126 °C (0.5 torr); IR (neat) 1710, 1095, 1020 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 4.10 (t, 3 H), 4.00 (t, 3 H), 2.77 (s, 2 H), 2.14 (s, 3 H), 1.43 (s, 3 H), 1.23 (t, 3 H), 1.20 (t, 3 H). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 56.98; H, 7.66.

3-Carbethoxy-3,4-dimethylbutyrolactone (10a and 10b). Sodium borohydride (0.1926 g, 0.0051 mol) was added in one portion to an ethanolic solution (10 mL) of diethyl 2-acetyl-2-methylsuccinate (**9**) (2.3 g, 0.010 mol) and stirred under argon at room temperature for 1 h. The reaction was added to water (100 mL) and extracted with ether (3 × 50 mL). The ether washings were combined and washed with saturated bicarbonate (1 × 50 mL) and brine (1 × 50 mL). The ether solution was dried over $MgSO_4$ and the solvent was removed by rotoevaporation to leave a mixture of the two lactones, **10a** and **10b**. The mixture was separated by MPLC on silica gel by using 3:1 v/v hexane/ethyl acetate as the eluant. The fastest moving component (R_f 0.33; 2:1 v/v hexane/ethyl acetate) was shown to be the cis lactone **10b** (vide infra). The next component (R_f 0.26) was the trans lactone **10a**. The total yield of lactone (**10a** plus **10b**) was 0.826 g (44%) with the ratio of **10b** to **10a** being 0.6.

10b: IR (neat), 1780, 1725, 1295, 1210, 1067, 942 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 4.65 (q, 1 H), 4.11 (q, 2 H), 3.06 (d, 1 H), 2.33 (d, 1 H), 1.14–1.40 (m, 9 H); ^{13}C NMR (67.8 Hz, $CDCl_3$) δ 173.6, 172.5, 79.5, 61.0, 48.4, 39.9, 16.9, 14.4, 13.5. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.99; H, 7.85.

10a: IR (neat) 1785, 1725, 1275, 1210, 1182, 1078, 940 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 4.29 (q, 1 H), 4.11 (q, 2 H), 2.97 (d, 1 H), 2.34 (d, 1 H), 1.13–1.37 (m, 9 H); ^{13}C NMR (67.8 Hz, $CDCl_3$) δ 173.8, 171.7, 82.0, 60.5, 49.2, 38.8, 20.1, 14.8, 13.2. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.73; H, 7.86.

3-Carboxy-3,4-dimethylbutyrolactone (11a and 11b). The hydrolysis of esters **10a** and **10b** was conducted according to the method of Loev.[19] The ester **10b** (0.3291 g, 0.0177 mol) was added to 90% formic acid (3 mL) containing methanesulfonic acid (0.2203 g, 0.0229 mol). The solution was stirred for 70 h under argon while maintaining a temperature of 85 °C. After cooling, the reaction was saturated with solid sodium chloride and extracted with ether (3 × 10 mL). The ether layers were combined, dried ($MgSO_4$), and rotoevaporated under aspirator pressure to leave **11b** which was recrystallized from toluene to afford 0.247 g (80%) of a white solid. The acid **11a** was prepared similarly from **10a** in 71% yield. **11b**: mp 113.5–115 °C; IR (KBr) 1720 (very broad), 1250, 1200, 1131, 1049, 947, 835, 680, 670 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) see Table II; ^{13}C NMR (67.8 MHz, $CDCl_3$) see Table II. Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37; O, 40.46. Found: C, 53.37; H, 6.03; O, 39.92.

11a: mp 105.5–107 °C; IR (KBr) 1770, 1690, 1290, 1231, 1071, 935, 669; ^1H NMR (270 MHz, $CDCl_3$) see Table II; ^{13}C NMR (67.8 MHz, $CDCl_3$) see Table II. Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37; O, 40.46. Found: C, 53.03; H, 6.13, O, 39.99.

Polymerization of 2b. 1-Vinyl 4-methyl itaconate (**2b**) (1.94 g, 0.0114 mol), AIBN (0.0862 g, 0.00053 mol), and dimethyl adipate (1.74, 0.010 mol) were weighted into a 5-mL volumetric flask under nitrogen in a glovebag. Enough ethyl acetate was added to bring the total volume to 5 mL. This solution was transferred via syringe to a flask that had been purged with nitrogen and equilibrated in a 50 °C water bath. The progress of the polymerization was monitored by GC by comparing the change in peak area of **2b** relative to that of dimethyl adipate. The reaction was quenched by adding the polymerization solution to an excess of diethyl ether (100 mL). If the quenching was done before 20% conversion of **2b**, the resulting polymer could be purified by redissolving in chloroform and reprecipitating from diethyl ether. The molecular weight (HPLC gel permeation chromatography; polystyrene) was 80 000 Daltons: IR (KBr) 1740, 1640, cm^{-1}; ^{13}C NMR (67.8 Hz, $CDCl_3$) δ 171.8, 170.7, 141.2, 98.3, 51.5, 45 (br), 35 (br).

Polymerization of 3a. 4-Vinyl itaconic acid (**3a**) (5.0 g, 0.032 mol) and AIBN (1.57 g, 0.00096 mol) were dissolved in 160 mL of chlorobenzene. This solution was degased by three freeze–

(18) Ethyl acetosuccinate was prepared according to the method of Adkins, H.; Isbell, N.; Wojcik, B. *Organic Syntheses*; Wiley: New York, 1953; Collect. Vol. II, p 262.

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pump-thaw cycles using argon as the inert atmosphere and then heated at 70 °C. After 20% reaction as determined by GC, the volatiles were removed under vacuum to afford 5 g of a jellylike material which was extracted with diethyl ether until a white powder remained. The powder was purified by redissolving in THF followed by precipitation with hexane. The weight of polymer recovered was 1.0 g and the molecular weight was 10000 Daltons (HPLC gel permeation chromatography; polystyrene standards): IR (KBr) 1780, 1720 cm^{-1}; ^{13}C NMR see Table II. Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.32; H, 5.39.

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Registry No. **2b**, 102634-12-8; **2b** (homopolymer), 102634-13-9; **3a**, 85753-88-4; **3a** (homopolymer), 85947-43-9; **3b**, 102651-51-4; **6**, 7338-27-4; **8**, 102651-52-5; **9**, 13668-05-8; **10a**, 102651-53-6; **10b**, 102651-54-7; **11a**, 102651-55-8; **11b**, 102651-56-9; vinyl acetate, 108-05-4; itaconic anhydride, 2170-03-8; trichloroethanol, 115-20-8; 1-methyl 4-trichloroethyl itaconate, 102651-57-0; itaconic acid, 97-65-4; ethyl acetosuccinate, 1115-30-6; methyl iodide, 74-88-4.

The Oxidative Decarboxylation of *N*-Aroylglycines to *N*-(Acetoxymethyl)benzamides and *N*-Formylbenzamides with Lead(IV) Acetate[1]

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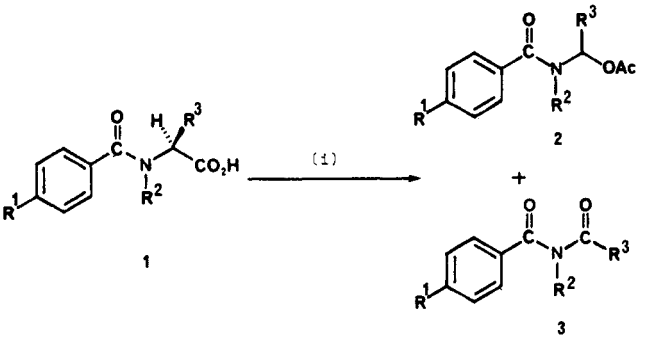
Treatment of *N*-aroylglycines that do not bear a strong electron-withdrawing substituent with lead(IV) acetate in acetic acid/acetic anhydride mixtures at 60–100 °C rapidly gives the corresponding *N*-(acetoxymethyl)benzamides and *N*-formylbenzamides in moderate yields after chromatography. These compounds are of interest in the study of the metabolism of xenobiotic *N*-methylbenzamides. *N*-(4-Nitrobenzoyl)glycine gives only *N*-(acetoxymethyl)-4-nitrobenzamide. 4-Chloro-*N*-methylbenzamide, *N*-aroylproline, and esters of *N*-aroylglycines are unaffected. Deuterium incorporation and other studies are consistent with a mechanism involving initial ligand exchange at lead followed by N-acetoxylation. Decarboxylation and elimination then ensue; final readdition of acetic acid to *N*-aroylimines leads to the observed products.

Many *N*-methyl-containing drugs and other compounds are metabolized to the corresponding *N*-hydroxymethyl analogue by preparations of murine liver.[2] The antitumor agent hexamethylmelamine,[3] the herbicide Monuron [*N*-(4-chlorophenyl)-*N'*,*N'*-dimethylurea],[4] and the common industrial solvent *N*,*N*-dimethylformamide[1] have been shown to be C-hydroxylated metabolically in vitro or in whole animals. The generated *N*-hydroxymethyl moieties are then either excreted as such or undergo further enzymic metabolism or intracellular chemical reaction. The relatively labile *N*-hydroxymethylamines may hydrolyze to give formaldehyde, a mutagen; while *N*-hydroxymethylbenzamide is sufficiently stable to be a substrate for further oxidation by cytosolic enzymes to *N*-formylbenzamide.[5] Hepatic metabolites containing the carbinolamine group may also act as electrophiles, either through the intermediacy of a small equilibrium concentration of the corresponding iminium ion or imine (recently reviewed[6]) or through biological derivatization of the alcohol (e.g., acetylation) which enhances its leaving group ability. We therefore sought a general preparation of *N*-(acetoxymethyl)benzamides and *N*-formylbenzamides as reference compounds for metabolic work and for study of their chemical reactivity in order to predict their biochemical reactions with cellular nucleophiles. Although *N*-(acetoxymethyl)benzamide (**2a**) has been prepared by acetylation of *N*-(hydroxymethyl)benzamide[7] and benzamide can be N-formylated with difficulty,[5] the present method furnishes both desired products from one reaction on one substrate. The oxidative decarboxylation of *N*-benzoylglycine (**1a**) by treatment with lead(IV) acetate to *N*-(acetoxymethyl)benzamide has been briefly reported by Süs and Rosenberger,[8] although the product was not well characterized. this paper now describes the results of our investigation into this reaction as regards synthetic utility, scope, limitations, and mechanistic pathway.

Scheme I. The Oxidative Decarboxylation of *N*-Aryl Amino Acids[a]



[a] (i) $Pb(OAc)_4/AcOH/Ac_2O$.

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