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CYCLOADDITION OF ISOPROPYLIDENE METHYLENEMALONATE TO ISOSAFROLE AND ANALOGUES

Robert Stevenson* and James V. Weber

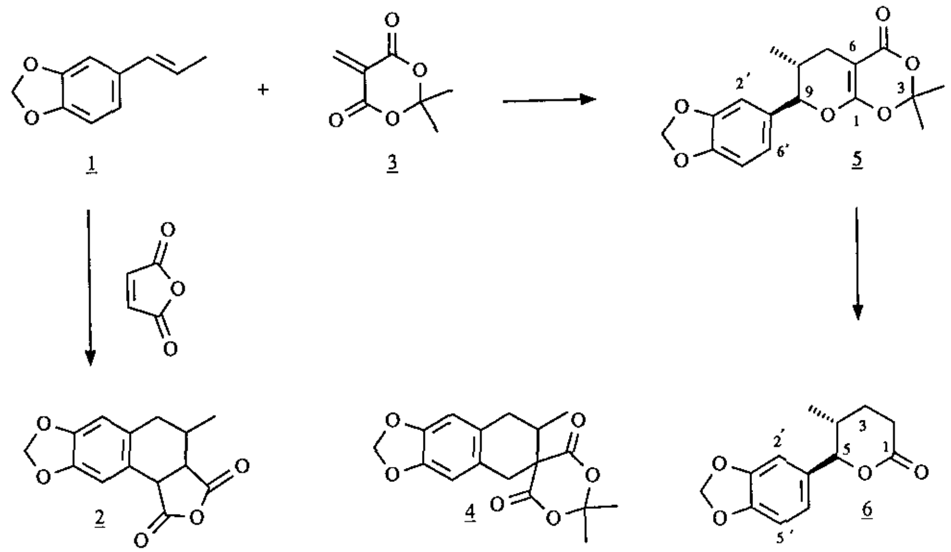
Department of Chemistry, Brandeis University, Waltham, MA 02254, U.S.A.

Abstract —— Isopropylidene methylenemalonate (methylene Meldrum's acid) serves as a heterodiene, rather than dienophile in 1:1 adduct formation at room temperature with isosafrole, styrene and p-methoxystyrene The resultant aryltrioxabicyclo[4.4.0]dec-1(6)-en-5-one heterocyclic products are degraded under mild hydrolytic conditions to yield the corresponding δ-aryl-δ-valerolactone or 5-arylpent-4-enoic acid.

In a study of dienophile addition to substituted styrenes, Hudson and Robinson[1] found that isosafrole (1) reacted with maleic anhydride in refluxing xylene to give the simple Diels-Alder adduct (2). Although diethyl maleate and diethyl acetylenedicarboxylate gave analogous adducts, the reaction appeared to be of limited scope since it failed with acraldehyde and p-benzoquinone as dienophiles. Additionally, the formation of 1:1 adducts is severely restricted by the effect of substituents on the styrene unit.

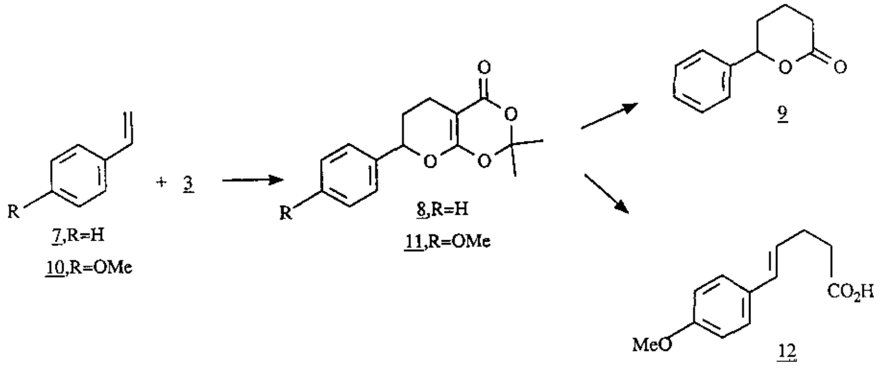
5-Arylidene and 5-alkylidene derivatives of Meldrum's acid are readily prepared,[2] have been recognized as excellent dienophiles[3] and used as intermediates in natural product synthesis.[4,5] The simplest alkylidene derivative, isopropylidene methylenemalonate (3) is a transient species readily trapped by dienes.[6,7] A recently reported facile procedure for generation of (3)[7] prompted our investigation of the reaction with isosafrole (1) in the hope that the enhanced dienophile reactivity would provide a general route to tetralins (e.g. 1 + 3 ⟶ 4 and/or regioisomer) and subsequently applicable to synthesis of natural lignans of the arylnaphthalene and aryltetralin classes.

In this connexion, we now find that isosafrole (1) reacts with (3) at room temperature to yield in 70% yield a 1:1 adduct which, however, does not have the analogous Diels-Alder product structure (4). Instead, the product to which we attribute structure (5), has been formed by a cycloaddition in which the diene-dienophile roles have been reversed, i.e., the styrene acts as dienophile and methylene Meldrum's acid serves as a heterodiene.



In support of structure (5), the pmr spectrum revealed the essential functionality, including non-equivalent isopropylidene methyl groups, a secondary methyl group, a benzylic ether proton, three additional alicyclic protons, a methylenedioxyphenyl group and three aryl protons. The ir and uv spectra are in accord with the chromophores present. The 2,4,10-trioxabicyclo[4.4.0]dec-1(6)-en-5-one heterocyclic moiety incorporated in (5) has previously been reported in products formed from reaction of electron-rich olefins (vinyl ethers, ketene acetals) with 5-alkylidene derivatives of Meldrum's acid^{8} or by intramolecular cycloadditions.$^{9-11}$

The adduct (5) proved to be labile and attempted recrystallization from common solvents resulted in a degradation which, however, was synthetically useful; thermally, or under a variety of hydrolytic conditions, (5) yielded the arylvalerolactone (6) in excellent yield.



The reaction of styrene (7) with methylene Meldrum's acid (3) under the same conditions gave in 80% yield the analogous adduct (8) which was readily hydrolyzed to the known product, phenylvalerolactone (9). Similarly, p-methoxystyrene (10) gave the expected adduct (11) which on hydrolysis yielded, interestingly, the aryl pentenoic acid (12) rather than the corresponding lactone.

The use of these procedures for syntheses of natural lactones is being investigated.

EXPERIMENTAL

Reaction of Isosafrole with Isopropylidene Methylenemalonate (5-Methylene-2,2-dimethyl-1,3-dioxane-4,6-dione, "Methylene Meldrum's Acid").

Proline (0.1 g) and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (1.44 g; 10 mmole) were added to a stirred solution of isosafrole (1.45 g; 10 mmole) in acetonitrile (10 ml). Aqueous formaldehyde (37%, 1 ml) was then added to give a turbid yellow suspension, which changed to a clear yellow solution after 5 min. The mixture was stirred at room temperature for 1 h, then poured on to ice to yield an oily precipitate which solidified during ice melting. Filtration gave the adduct, trans-,9-(3,4-methylenedioxyphenyl)-3,3,8-trimethyl-2,4,10-trioxabicyclo-[4,4,0]dec-1(6)-en-5-one (5) as a white solid (2.26 g, 71% yield), mp 110-111°C. Since this product could not be recovered unchanged on attempted recrystallization (warming in a variety of solvents), the analytical sample was dried *in vacuo* at room temperature (Anal Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.4, H, 5.9). Pmr ($CDCl_3$): δ 0.84 (d, J = 6.3 Hz, C-8 Me), 1.71 (s, C-3 Me), 1.74 (s, C-3 Me), 2.09-2.16 (2H, m, H-7 and 8), 2.57 (d, J = 10.1 Hz, H-7), 4.65 (d, J = 10.6 Hz, H-9), 5.98 (s, $-OCH_2O-$) and 6.78 (br.s, 3 ArH). ^{13}C-nmr ($CDCl_3$)· δ 16.9 (C-8 Me), 17.0 (8-C), 24.2 (C-3 Me), 26.2 (C-8 Me), 33.2 (7-C), 77.7 (6-C), 87.7 (9-C), 101.2 (OCH_2O), 105.9 (3-C), 107.0 (5'-C), 108.1 (2'-C), 121.4 (6'-C), 130.6 (1'-C), 148.05 (4'-C), 148.1 (3'-C), 163.2 (5-C) and 164.3 (1-C). Uv (CH_3CN): λ 242 (8200), 259 (6200) and 285 (5400) nm. Ir ($CHCl_3$) 1710 (C=O) and 1635 (C=C) cm^{-1}.

When this experiment was repeated with proline absent, clarification of the solution required 15 min, but the same adduct (67% yield) was isolated with identical work-up after 1 h.

trans-5-Methyl-6-(3',4'-methylenedioxyphenyl)-tetrahydro-2H-2-pyran-2-one (6) from Isosafrole Adduct (5).

(a) A solution of the adduct (5) (0.38 g) in acetonitrile (5 ml) was added to water (50 ml) and boiled to a volume of *ca.* 10 ml. The cooled solution was extracted with ether (3 x 25 ml) and the dried ($MgSO_4$) extract evaporated under reduced pressure to give a residual oil which on trituration with light petroleum yielded the valerolactone (6) as a colourless solid (0.27 g), mp 67-70°C. (Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.35; H, 6.1). Pmr ($CDCl_3$): δ 0.84 (d, J = 6 Hz, Me), 1.65 (m, H-5), 1.99 (2H, m, H-3), 2.68 (2H, m, H-2), 4.75 (d, J = 10 Hz, H-6), 5.98 (s, $-OCH_2O-$) and 6.78 (m, 3H, ArH). ^{13}C-nmr ($CDCl_3$): δ 17.0 (C-5

Me), 27.7 (4-C), 29.7 (3-C), 34.0 (5-C), 88.1 (6-C), 101.2 (OCH_2O), 107.2 (2'-C), 107.9 (5'-C), 121.2 (6'-C), 132.2 (1'-C), 147.7 (4'-C), 147.8 (3'-C) and 171.7 (1-C). Uv (CH_3CN) 236 (5100) and 286 (4500). Ir ($CHCl_3$) 1728 (C=O) cm^{-1}.

(b) A solution of the adduct (5) (159 mg) and potassium hydroxide (1.5 g) in water (2.5 ml) and 2-ethoxyethanol (10 ml) was heated under reflux for 27 h, then concentrated under reduced pressure. Water (10 ml) was added and the mixture extracted with ether. The aqueous phase was then acidified with hydrochloric acid (10%) and re-extracted with ether. Evaporation of this dried extract gave an oil which solidified on trituration with light petroleum to give the lactone (0.11 g), mp 65-67°C, with spectra identical to (a) above.

(c) The adduct (5) (50 mg) was heated under reflux overnight with 6N hydrochloric acid, then cooled and extracted with ether (3 x 50 ml). Evaporation of the dried extract yielded the lactone (30 mg) as a colourless solid, mp 65-67°C.

(d) The adduct (5) (200 mg) was heated at 180-185°C (oil bath) for 3 h. The resultant brown oil was dissolved in ether, and the water-washed and dried extract evaporated to yield the lactone (120 mg), mp 64-67°C.

Reaction of Styrene with Isopropylidene Methylenemalonate.

Meldrum's acid (1.44 g) was added to a stirred solution of styrene (1.04 g) in acetonitrile (10 ml), followed by aqueous formaldehyde solution (1 ml, 37%). The reaction mixture (cloudy after 2 min and clarified after 10 min) was stirred at room temperature for 1 h, then poured on to ice to give an oily precipitate. The mixture was extracted with ether (3 x 25 ml), dried and evaporated to give 9-phenyl-3,3-dimethyl-2,4,10-trioxabicyclo[4.4.0]dec-1(6)-en-5-one (8) as a foam solid (2.06 g). Pmr ($CDCl_3$): δ 1.74 (s, C-3 Me), 1.76 (s, C-3 Me), 2.06-2.23 (2H, m, H-8), 2.40-2.52 (2H, m, H-7), 5.20 (dd, J = 2,10 Hz, H-9) and 7.36-7.38 (m, 5 ArH). Ir ($CHCl_3$) 1715 (C=O) and 1630 (C=C) cm^{-1}.

Without further purification, this adduct (0.50 g) was heated under reflux for 2 h with acetonitrile (5 ml)-water (50 ml). Work-up by ether extraction in the usual way gave an oil (0.23 g) which crystallized from ether to give 6-phenyl-tetrahydro-2H-2-pyran-2-one (5-phenyl-5-hydroxypentanoic acid lactone) (9) as a solid (0.2 g), mp 74-75°C (lit.,[12] mp 74-76°C). Pmr ($CDCl_3$): δ 1.71 (2H, m, H-5), 1.90 (2H, m, H-4), 2.67 (2H, m, H-3), 5.30 (m, H-6) and 7.36 (br.s, 5 ArH). Ir ($CHCl_3$) 1730 (C=O) cm^{-1}.

Reaction of p-Methoxystyrene with Isopropylidene Methylenemalonate.

Meldrum's acid (1.44 g) and p-methoxystyrene (1.34 g) were reacted as for previous adduct formation experiments. The product, 9-(4'-methoxyphenyl)-3,3-dimethyl-2,4,10-trioxabicyclo

[4.4.0]dec-1(6)-en-5-one (11) was isolated as a colourless solid (2.5 g), mp 89°C after ether solvent removal. Pmr ($CDCl_3$): δ 1.75 (s, two C-3 Me), 2.11-2.19 (2H, m), 2.40-2.51 (2H, m), 3.82 (s, OMe), 5.14 (dd, J = 2,10 Hz, H-9), 6.89 (d, J = 9 Hz, H-3',5') and 7.28 (d, J = 9 Hz, H-2',6').

The adduct (11) (100 mg) was heated in aqueous acetonitrile in the usual way and the product crystallized from diethyl ether to give 5-(p-methoxyphenyl)-pent-4-enoic acid (12) as a solid (70 mg), mp 112°C. (Found: M^+ 206.0934. $C_{12}H_{14}O_3$ requires M 206.0943). Pmr ($CDCl_3$) 2.45-2.54 (4H, m, H-2 and -3), 3.79 (s, OMe), 6.09 (1H, m, H-4), 6.39 (1H, d, J = 15 Hz, H-5), 6.85 (d, J = 9 Hz, H-3',5') and 7.25 (d, J = 9 Hz, H-2',6'). ^{13}C-nmr ($CDCl_3$): δ 28.2 (2-C), 34.2 (3-C), 55.6 (OCH_3), 113.9 (3',5'-C), 125.7 (5-C), 127.1 (2',6'-C), 127.7 (1'-C), 130.9 (4-C), 158.0 (4'-C) and 179.0 (1-C). Ir (KBr) 3300-2500 (OH) and 1710 (CO_2H) cm^{-1}. The same product was obtained by acid or base hydrolysis.

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