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Some Reactions of 2-Methyl-1-phenylpropylidene-malononitrile in Sulfuric Acid/Alcohol

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The reaction of 2-methyl-1-phenylpropylidenemalononitrile with different alcohols using sulfuric acid as co-reactant is investigated. The products are α-methoxycarbonyl-γ,γ-dimethyl-β-phenyl-γ-butyrolactone from methanol, 2-methyl-1-phenyl-1-propanone and diethyl malonate from ethanol and *N*,*N*-diisopropyl-2-methyl-1-phenylpropylidenemalonamide from isopropyl alcohol. A reaction mechanism for the formation of the butyrolactone is suggested, substantiated by NMR and deuteration experiments.

Ketones are generally less reactive than aldehydes in the Knoevenagel condensation. The rate and yields depend on the nature of the methylene compound and the steric hindrance to condensation.[1] The yields of condensation products in the reaction of aromatic ketones with diethyl malonate in the presence of titanium tetrachloride and pyridine in tetrahydrofuran are reported to be good [2] even in cases where the usual condensation methods [1] are unsuccessful. However, condensation of 2-methyl-1-phenyl-1-propanone with dimethyl malonate under these conditions gave only low yields (15 %) of dimethyl 2-methyl-1-phenylpropylidenemalonate (*2*). The corresponding malononitrile *1* was readily available by the reaction of 2-methyl-1-phenyl-1-propanone with malononitrile in glacial acetic acid in the presence of anhydrous ammonium acetate.[3] Since alcoholysis of nitriles to esters is known to proceed in the presence of anhydrous hydrogen chloride,[4] sulfuric acid [5] or arenesulfonic acids,[6] attempts were made to obtain better yields of malonate *2* by treating malononitrile *1* with different alcohols using sulfuric acid as co-reactant.

Treatment of malononitrile *1* with an equimolar solution of sulfuric acid in methanol did not give malonate *2*, but a compound showing IR absorptions at 1770 cm^{-1} (saturated γ-lactone) and 1725 cm^{-1} (unconjugated ester). The NMR spectrum shows that only one methyl ester group is present. IR and NMR data were in agreement with α-methoxycarbonyl-γ,γ-dimethyl-β-phenyl-γ-butyrolactone (*3*). No molecular ion was observed in the mass spectrum. The fragmentation pattern below *m/e* 162 (base peak) is similar to that observed for methyl cinnamate,[7] and may be explained by the expulsion of fragment $C_4H_6O_2$ from the molecular ion of the lactone to give methyl cinnamate *m/e* 162 (M − 86, 100).

In compound *3* the phenyl and methoxycarbonyl groups most likely are in the *trans* position as no isomerization occurred when *3* was treated with sodium methoxide in methanol.

In addition to lactone *3*, small quantities of another crystalline compound were isolated. The structure *4* of this product is based on the following data.

The IR spectrum (KBr) shows a band at 3320 cm^{-1} due to the N−H bond, strong absorptions at 1620 and 1585 cm^{-1}, one of them being the carbon-carbon double bond and a strong lactone carbonyl band as low as 1680 cm^{-1}. In comparison, *5* shows carbonyl absorption at 1718 cm^{-1} ($CHCl_3$).[8] Having in mind the possibility of intramolecular hydrogen bonding * in *4* and the further substitution of

* *N*-Methyl anthranilate shows a carbonyl absorption at 1685 cm^{-1}, the carbonyl frequency of methyl *N*,*N*-dimethylanthranilate being the normal ester value of 1730 cm^{-1}.[9]

a methoxy group on the carbon-carbon double bond, a lactone carbonyl frequency at 1680 cm^{-1} seems reasonable.

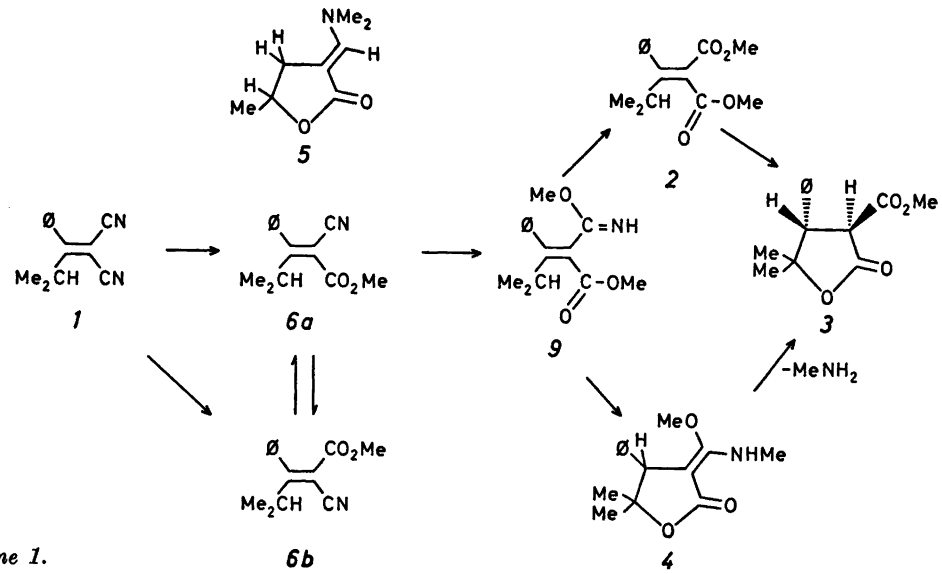
The UV spectrum of compound *4* (λ_{max} 278 nm, ε 19 500 (MeOH)) indicates the presence of a conjugated system. NMR data were in agreement with structure *4*. The methyl doublet at δ 2.93 (J 5.5 Hz) degenerated into a sharp singlet on the addition of D_2O/DO^-, in accordance with the expected behaviour of a secondary amine function. MS of compound *4* gave a base peak at m/e 261 corresponding to the molecular ion, shown by high-resolution MS to have the composition $C_{15}H_{19}O_3N$.

Malononitrile *1* has been shown to cyclize in concentrated sulfuric acid to a mixture of the isomeric compounds 2-carbamoyl-3-isopropyl-1-indenone and 2-carbamoyl-3-isopropylidene-1-indanone,[3] but by use of 80 % sulfuric acid/methanol *3* was the main product. No derivative of indenone and/or indanone was formed, showing the great tendency of this system for lactone formation. A decrease in concentration of sulfuric acid to 30 % had no influence on the reaction, but when the concentration was lowered to 20 % a mixture of six compounds was obtained (GLC): Dimethyl 2-methyl-1-phenylpropylidenemalonate (*2*) (8 %), *3* (14 %), methyl (*E*)-2-cyano-4-methyl-3-phenyl-2-pentenoate (*6a*) (16 %) and the corresponding *Z* isomer *6b* (20 %), 2-methyl-1-phenyl-1-propanone (*7*) (9 %) and dimethyl malonate (*8*) (4 %) besides unreacted malononitrile *1*. Compounds *2*, *3*, *7* and *8* were identified by GLC comparison with authentic samples, whereas compounds *6a* and *6b* were isolated by preparative GLC. Configuration assignments of pentenoates *6* were made by NMR on the basis of the different chemical shift of the methoxycarbonyl groups in these two isomers.[10]

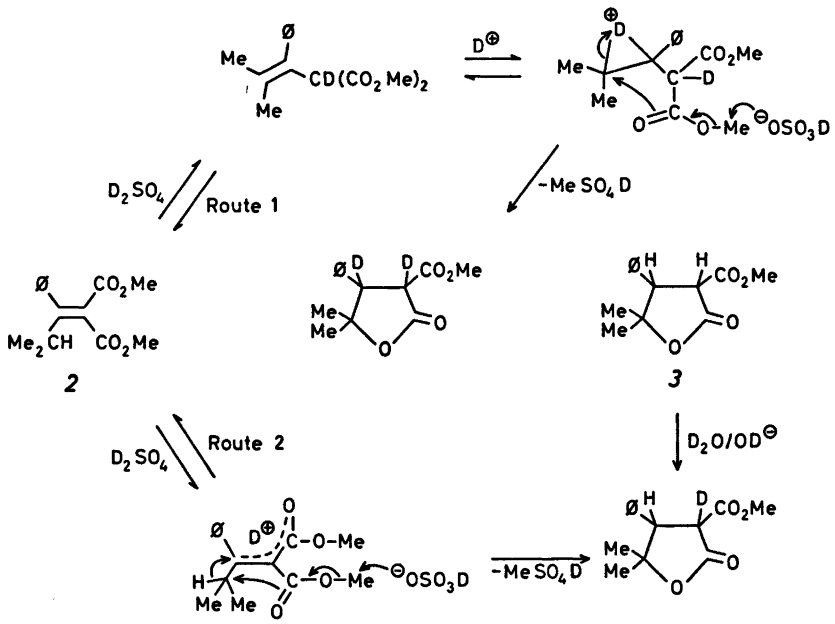
The ketene *O*,*N*-acetal *4* is most likely formed from *9* by a concerted ring closure, double bond migration and a nitrogen attack on the ester methyl group, the latter part of the reaction bearing some similarity to the "Pinner cleavage".[11] However, if *4* were the main precursor to *3*, methylamine should be found as a product from this transformation,[12,13] but as shown in the experimental part, the only nitrogen base found in the equimolar reaction is ammonia. Thus the formation of *4* represents a side reaction (Scheme 1).

Direct lactonization of *6a* is not very likely since no cyanolactone analogous to *3* is observed.

Formation of *3* in good yield on treatment of *2* with a solution of 20 % sulfuric acid in methanol shows that *2* may be the precursor of the lactone. On addition of concentrated sulfuric acid to *2* at room temperature a rapid transformation to *3* (75 %) occurred. In addition, a yellow compound most likely being 3-isopropyl-2-methoxycarbonyl-1-indenone (25 %)



Scheme 1.



Scheme 2.

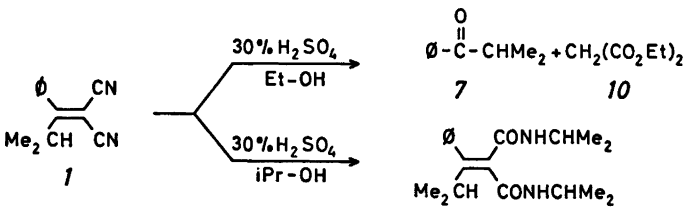
was isolated, an analogy to the formation of 2-carbamoyl-3-isopropyl-1-indenone from malononitrile *1* in concentrated sulfuric acid.[3] When the lactonization process was followed by NMR, a signal corresponding to methyl sulfate was detected, consistent with nucleophilic attack by sulfate anion on the methoxycarbonyl group. Minor amounts of dimethyl ether, obtained in the equimolar reaction of malononitrile *1* with sulfuric acid/methanol, is probably the result of competing nucleophilic attack of methanol on the ester methyl group during the ring closure.

Two different reaction routes for the formation of *3* from *2* are possible (Scheme 2): migration of a carbon-carbon double bond prior to the ring closure reaction (Route 1) or ring closure involving a hydride shift (Route 2). Treatment of *2* with deuterated concentrated sulfuric acid gave a mono deuterated lactone having exactly the same NMR spectrum as the product formed by treatment of *3* with D_2O/DO^-. A mechanism involving a hydride shift is in agreement with this experimental result.

Nucleophilic attack by sulfate anion on the methyl ester group in *2*, followed by a hydride shift in the cyclization process, is the most plausible way to explain the formation of *3* from malononitrile *1*.

Treatment of malononitrile *1* with a 30 % solution of sulfuric acid in ethanol mainly resulted in attack on the carbon-carbon double bond to give the cleavage products 2-methyl-1-phenyl-1-propanone (*7*) and diethyl malonate (*10*).

The use of isopropyl alcohol instead of ethanol gave malonamide derivative *11* in good yield (65 %) due to the attack of isopropyl cation on the nitrile groups (Ritter reaction) [14] (Scheme 3).



Scheme 3.

EXPERIMENTAL

General. Melting points (uncorrected) were determined on a micro hot-stage. IR spectra were recorded on a Perkin-Elmer 457 Grating infrared Spectrophotometer, NMR spectra on a Varian A-60A Spectrometer in $CDCl_3$ and the mass spectra on an AEI MS 902 instrument. Elemental analyses were performed by I. Beetz, West-Germany.

Dimethyl 2-methyl-1-phenylpropylidenemalonate (2). Absolute THF (500 ml) was added to a solution of titanium(IV) chloride (33 ml, 0.3 mol) in absolute CCl_4 (76 ml) under nitrogen at 0 °C. 2-Methyl-1-phenyl-1-propanone (22.2 g, 0.15 mol) and dimethyl malonate (19.8 g, 0.15 mol) were added to the mixture, followed by slow addition of absolute pyridine (48 ml, 0.6 mol) in absolute THF (100 ml) at 0 °C. The mixture was stirred at 25 °C for 48 h, refluxed for 24 h and hydrolyzed by adding water (150 ml) to give, after work-up with ether, compound *2*. The product was distilled and recrystallized from pentane at −20 °C, yield 5.9 g (15 %) b.p. 100 °C/0.02 mmHg. Anal. $C_{15}H_{18}O_4$: C, H. MS: *m/e* 262 (M^+). ^1H NMR: δ 6.9−7.5 (5 H, m), 3.82 (3 H, s), 3.40 (3 H, s), 3.55 (1 H, m), 1.05 (6 H, d, *J* 7 Hz).

Reactions of 2-methyl-1-phenylpropylidenemalononitrile (1) with sulfuric acid/alcohol. General procedure. A solution of *1* in sulfuric acid/alcohol was kept at 90−100 °C for 3.5−56 h, poured on ice and extracted into ether or chloroform. The organic layer was washed with water, sodium bicarbonate, water and dried over $MgSO_4$. After removal of the solvent the products were recrystallized, distilled or identified by GLC.

In 57 % sulfuric acid/methanol (v/v, equimolar). Malononitrile *1* (10 g, 51 mmol), concentrated H_2SO_4 (98.1 g, 1 mol) and MeOH (32 g, 1 mol) were heated for 3.5 h (~5 mmol of dimethyl ether was collected) to give *α-methoxycarbonyl-γ,γ-dimethyl-β-phenyl-γ-butyrolactone (3)*, yield 7.0 g (55 %), m.p. 127−128 °C (MeOH). Anal. $C_{14}H_{16}O_4$: C, H. MS: *m/e* 162 (M−86, 100), 161 (20), 131 (70), 103 (24). ^1H NMR: δ 7.35 (5 H, broad s), 4.19 (1 H, d, *J* 13 Hz), 4.01 (1 H, d, *J* 13 Hz), 3.75 (3 H, s), 1.60 (3 H, s), 1.08 (3 H, s). IR (KBr): 1770 and 1725 cm^{-1}, *lactone 4*, yield 0.1 g (0.8 %), m.p. 167 °C (MeOH). MS: *m/e* 261 (M^+, 100), $C_{15}H_{19}O_3N$. ^1H NMR: δ 7.0−7.5 (5 H, m), 3.96 (1 H, s), 3.48 (3 H, s), 2.93 (3 H, d, *J* 5.5 Hz), 1.53 (3 H, s) 0.90 (3 H, s). IR (KBr) 3320, 1680, 1620 and 1585 cm^{-1}. UV (MeOH):λ_{max} 278 nm, ε 19 500. In one experiment the acidic water solution was made alkaline with NaOH. On heating to 100 °C ~100 mmol of ammonia was collected.

In 80 % sulfuric acid/methanol (v/v). Treatment of malononitrile *1* with 80 % sulfuric acid/methanol in the same manner as described above gave *3* as the main product.

In 20 % sulfuric acid/methanol (v/v). Malononitrile *1* (10 g, 51 mmol), concentrated H_2SO_4 (25.5 g, 0.26 mol) and MeOH (41.6 g, 1.3 mol) were heated for 56 h. The following six compounds were obtained: *Dimethyl 2-methyl-1-phenylpropylidenemalonate (2)*, (8 %), α-methoxycarbonyl-γ,γ-dimethyl-β-phenyl-γ-butyrolactone (*3*), (14 %), methyl (*E*)-2-cyano-4-methyl-3-phenyl-2-pentenoate (*6a*), (16 %). This product was isolated by prep. GLC and the boiling point of the liquid was difficult to obtain. MS: *m/e* 229 (M^+, 100). ^1H NMR: δ 7.0−7.6 (5 H, m), 3.88 (3 H, s), 1.05 (6 H, d, *J* 7 Hz), the methin proton is poorly resolved. IR (film): 2220 and 1730 cm^{-1}, *methyl (Z)-2-cyano-4-methyl-3-phenyl-2-pentenoate (6b)*, (20 %), m.p. 97−99 °C (MeOH). MS: *m/e* 229 (M^+, 100). ^1H NMR: δ 6.8−7.5 (5 H, m) 3.60 (3 H, s), 3.2−3.7 (1 H, m), 1.11 (6 H, d, *J* 7 Hz). IR ($CHCl_3$): 2220 and 1740 cm^{-1}. Found: C 72.87; H 6.48. Calc. for $C_{14}H_{15}O_2N$: C 73.36; H 6.55, *2-methyl-1-phenyl-1-propanone (7)*, (9 %) and *dimethyl malonate (8)*, (4 %) were identified by GLC on comparison with authentic samples.

In 30 % sulfuric acid/ethanol (v/v). Malononitrile *1* (2.5 g, 13 mmol) and 30 % H_2SO_4/EtOH (50 ml) were heated for 24 h to give mainly *2-methyl-1-phenyl-1-propanone (7)* and diethyl malonate (*10*), identified by GLC on comparison with authentic samples.

In 30 % sulfuric acid/isopropyl alcohol (v/v). Malononitrile *1* (2.5 g, 13 mmol) and concentrated H_2SO_4/isopropyl alcohol (50 ml) were heated for 25 h to give N,N-*diisopropyl-2-methyl-1-phenylpropylidene malonamide (11)*, yield 2.6 g (63 %), m.p. 207 °C (C_2H_5). Anal. $C_{19}H_{28}O_2N_2$: C, H. MS: *m/e* 316 (M^+, 17). ^1H NMR: δ 6.8−7.5 (5 H, m), 5.0−5.3 (2 H, broad s), 3.1−4.4 [3 H, m, $(Me)_2$ C*H*, NH-C*H*$(Me)_2$], 1.20 (6 H, d, *J* 6 Hz), 0.99 (6 H, d, *J* 7 Hz), 0.64 (6 H, d, *J* 6 Hz). IR (KBr): 3270, 1650, 1625 and 1530 cm^{-1}.

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