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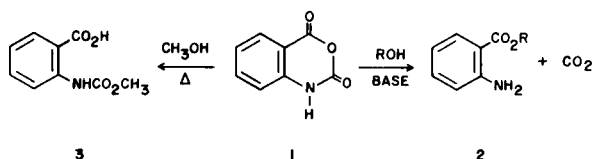
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A wide variety of alkyl isoatoates can be prepared in good yield from the high temperature reaction of isoatoic anhydride with alcohols. Isoatoates were found to undergo an apparent high temperature rearrangement reaction. Proposed reaction schemes are presented for the formation of isoatoates and the subsequent rearrangement reaction.

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Isoatoic anhydride (1) readily ring opens in the presence of alcohols (2) and a base catalyst to give the corresponding anthranilates (2). A very different ring opened product,



methyl isoatoate (3) first reported (3) about eighty years ago, is obtained by reacting 1 with methanol at 140° in the absence of a base catalyst. This interesting isoatoic anhydride ring opening reaction has gone unstudied until a recent interest at Sherwin-Williams Chemicals in knowing the applicability and the mechanism of this uncatalyzed ring opening reaction. This report will disclose that

isoatoate formation is a general reaction and that isoatoates undergo at least two interesting high temperature reactions. Proposed reaction schemes for the formation of isoatoates and for one of the high temperature isoatoate reactions will also be presented.

The uncatalyzed reaction of alcohols with 1 at temperatures in excess of 100° was found to be general in scope. All tested alcohols from primary to tertiary gave isoatoates in yields as listed in Table I. Varying amounts of the corresponding anthranilates were also obtained in all instances except with *t*-butyl alcohol. In general, ethanol and isopropanol produced the least amount of anthranilate by-product and also gave the highest yields of isoatoate. The most consistent yields of isoatoate were obtained using dry solvent and recrystallized isoatoic anhydride.

A number of conditions were observed to increase the

Table I

Preparation of Isoatoates (a)

ROH	Reaction Temperature ($^\circ\text{C}$)	Reaction Time (hours)	Isoatoate	% Yield (b) Anthranilate	Other
Me	141	1	60	40	----
Et	161 (c)	2	60	33	----
	150	1	94	(k)	----
	125	1	98	(k)	----
	115	2	98	(k)	----
	99	5	18	64	----
<i>n</i> -Pr (d)	116	3	62	(k)	18 (e)
<i>n</i> -Bu (d)	161	2	62	25	----
2-Ethex (d)	152	1	95	(k)	----
	125	2	54	(k)	38 (e)
	170 (f)	1	----	52	40 (g)
	155 (h)	1	87	(k)	----
	120 (i)	1	(j)	9	----
Cyclohex (d)	161	1	75	(k)	----
<i>t</i> -Bu	170	4	41	----	39 (e)
2-HOEt (d)	145	1	17	----	(l)

(a) Reactions were carried out in a 300 ml. autoclave with an isoatoic anhydride-alcohol ratio of 0.05-0.06 moles/100 ml. (b) Crude yield. Product ratios were determined by nmr integration. (c) Reaction in sealed glass tubes. (d) Reaction in standard glassware. (e) Unreacted isoatoic anhydride. (f) Reacted with *N*-methylisoatoic anhydride. (g) Unreacted *N*-methylisoatoic anhydride. (h) Reacted with 5-chloroisoatoic anhydride. (i) Reacted with 5-nitroisoatoic anhydride. (j) Product was a mixture of isopropyl 5-nitroisoatoate and 5-nitroanthranilic acid. (k) Small, undetermined amounts of anthranilate. (l) Unidentified products.

amount of anthranilate or other unidentified by-products. Small amounts of water (up to 0.5 equivalent) can decrease isatoate yields by 25-30% and significantly increase the yields of undesirable side products. Catalytic amounts of a strong acid (such as sulfuric acid) also decreases the yield of isatoate and increases the amount of anthranilate collected. Increasing the isatoic anhydride concentration from 0.5M to 2.0M increased the relative amounts of anthranilate and unidentified by-products. Using technical grade 1, which contains trace amounts of acid or base impurities also increased the amount of anthranilate product and other by-products. Dilution of the isatoate reaction mixture with 50% by volume of dioxane (a solvent for isatoic anhydride) not only significantly decreased the rate of formation and yield of isatoate but also increased the amount of by-products.

For alcohols boiling below 95° an autoclave was used for the isatoate preparation reaction while standard glassware was used for alcohols which boil over 95°. As noted in Table I isatoates could also be prepared from the ring substituted materials, 5-chloro- and 5-nitroisatoic anhydride, however, *N*-methylisatoic anhydride gave only the corresponding anthranilate. The implications of this latter observation will be discussed in the part concerned with proposed reaction pathways.

Isatoates have some previously unreported interesting characteristics. During a crystallization of ethyl isatoate from ethanol-water or chloroform, a platelet crystal was obtained (isatoates usually crystallize in needles). The infrared and nmr spectra suggested that this new material was a half-hydrate of ethyl isatoate. Heating this new material at 110° for two hours removed the hydrated water leaving behind a material now identified by infrared

Table II

Melting Points of Isatoates (a)

Isatoate	M.p. (°C)	Lit. (c)
Methyl	180.2-181.0 (b)	181 (d)
Ethyl	123.0-124.5	126-128
<i>n</i> -Propyl	115.5-116.5	
<i>n</i> -Butyl	100.0-100.5	95-97
<i>i</i> -Propyl	182.5-184.0 (b)	182-184
<i>t</i> -Butyl	155.5-157.0 (b)	
Cyclohexyl	127.0-128.5	
2-Ethylhexyl	63.5-65.0	60.62
<i>i</i> -Propyl 5-chloro	199.5-201.5 (b)	
<i>i</i> -Propyl 5-nitro	193.0-197.0 (b)	
Methyl <i>N</i> -methyl	133.5-134.5	137-138 (e)
<i>i</i> -Propyl <i>N</i> -Methyl	108.0-110.0	

(a) Melting points uncorrected. (b) Corrected. (c) B. Blank, S. R. Cohen and D. W. Spiggle, *J. Chem. Eng. Data*, **13**, 577 (1968). (d) E. Erdmann, *Chem. Ber.*, **32**, 2159 (1899). (e) *Beilstein*, **14**, 347.

and nmr spectra as a second crystal form of ethyl isatoate. No other characterization of this apparent isatoate hydrate has been carried out.

Melting points for the various isatoates prepared are presented in Table II. The melting points of the methyl, isopropyl and *t*-butyl isatoates are unusually high in comparison with the other series members suggesting some unusual structural or conformational characteristics. Substitution of a methyl group on nitrogen apparently disturbs the usual conformation of intermolecular bonding as the *N*-methylisatoates follow a predictable melting point trend.

Table III

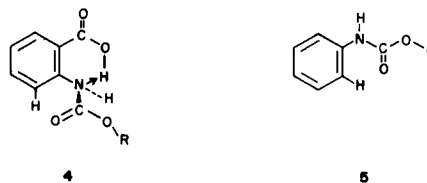
Characteristic Infrared and Nmr Absorption Bands for Isatoates

Isatoate	N-H	Ir (cm ⁻¹) (a)	C=O	NMR (b) δ, ppm
Methyl	3330		1750, 1660	8.5
<i>i</i> -Propyl	3320		1740, 1675	8.4
<i>i</i> -Propyl <i>N</i> -Methyl	3200 (c)		1720, 1672	7.2-7.6
<i>i</i> -Propyl 5-chloro	3330		1725, 1675	8.4
<i>t</i> -Butyl	3320		1740, 1680	8.4
Ethyl (I)	3320		1740, 1730, 1675	8.5
(II)	3320, 3290, 3220		1740, 1710, 1680	-----
Ethyl·½H ₂ O	3475, 3400, 3270		1710, 1675	8.5
2-Ethylhexyl	3325		1740, 1675	8.5
Methyl <i>N</i> -phenylcarbamate	3400		1730, 1705	7.0-7.5
Methyl Anthranilate	3475, 3370		1700	6.4-6.8
Anthranilic acid	3475, 3370		1675	6.4-6.9 (d)

(a) Infrared spectra of isatoates in mulls on sodium chloride plates, not corrected. (b) Nmr spectra of isatoates in deuteriochloroform (internal TMS) solution. Ring proton *alpha* to nitrogen atom. (c) Hydroxyl of acid group. (d) Perdeuteriodimethylsulfoxide solvent.

The infrared and nmr spectra (see Table III) also suggest that in general isatoates exist in unusual conformations in both the solid state and in solution. For example, in the nmr spectrum the aromatic ring proton *alpha* to the carbamate group of isatoates (4) is shifted downfield by almost 2 ppm from a proton *alpha* to the amino group of methyl anthranilate or anthranilic acid. This *alpha* proton is also shifted downfield by at least 1 ppm when compared with the *alpha* ring proton of methyl *N*-phenylcarbamate (5). The *ortho* carboxyl group of isatoates must cause a conformational change such that the carbamate carbonyl exerts a deshielding effect on the *alpha* proton by a through space field effect. Substitution of a methyl group on the carbamate nitrogen apparently destroys this special conformation effect resulting in the *alpha* proton now absorbing in nearly the same place as that observed for 5. The conformation change caused by methyl substitution on a carbamate nitrogen is also noted

to the infrared spectrum. The OH of the unsubstituted isatoate acid group is shifted from a very broad, 2500-3500 cm^{-1} , absorption to a more defined absorption at 3200 cm^{-1} for the *N*-methylisatoates.



The appearance of anthranilates in the isatoate products prompted a study to determine their source. Isatoates undergo little or no reaction when they are heated in alcohol under the reaction conditions used for isatoate synthesis. But continued heating at 150-180° for 5-7 hours showed that isatoates did undergo a very interesting reaction, an apparent rearrangement to anthranilates.

Table IV

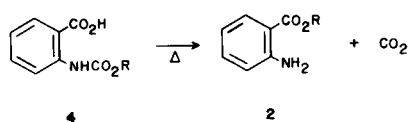
Rearrangement of Isatoates to Anthranilates (a)

Isatoate	Time (hours)	Temperature (°C)	Isatoate	% Products (j) Anthranilate	Other (h)
Methyl					
0.5	6	160	85	15	----
0.6	6	172	62	32	6
0.2	6	172	70	24	6
1.0	6	172	56	32	12
0.5 (b)	6	162	30	51	19
0.5 (o)	6	162	37	43	20
0.4 (c)	7	162	21	79	----
0.5 (d)	6	160	100	----	----
0.5 (b,k)	8	162	42	----	48 (l)
0.5 (e)	6	170	83 (g)	5	1
0.6 (b,i)	5	162	----	84	undet.
0.5 (m)	6	180	15 (n)	----	5
0.7 (f)	2	180	50	26	24
<i>i</i> -Propyl					
0.6	6	172	100	----	----
0.5 (c)	7	170	80	16	4
0.5 (b,p)	5	180	0	100	0
0.4 (c,q)	7	170	64	36	----
0.5 (r)	6	180	15 (s)	----	17
<i>t</i> -Butyl					
0.4 (c)	7.5	180	(h)	----	----

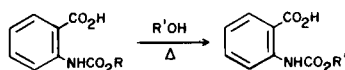
(a) Reactions in sealed glass tubes containing alcohol solvent which corresponds with isatoate. (b) Copper metal catalyst. (c) Triethylamine catalyst. (d) Chloroform solvent. (e) *t*-Butyl alcohol solvent. (f) Dimethylsulfoxide solvent. (g) Other product 11% *t*-butyl isatoate. (h) Mixtures of unidentified materials. (i) Methyl *N*-methylisatoate. (j) Mole percent of recovered products determined by nmr integration. (k) Diglyme solvent. (l) Remaining products isatoic anhydride plus unidentified materials. (m) 2-Propanol solvent. (n) Remaining product 80% isopropyl isatoate. (o) Iron powder catalyst. (p) Isopropyl *N*-methylisatoate. (q) Isopropyl 5-chloroisatoate. (r) Methanol solvent. (s) Remaining product 37% methyl isatoate and 31% methyl anthranilate.

Some examples of these rearrangements are presented in Table IV.

This rearrangement, depending on solvent and R group, was anywhere from 0 to 80% complete under the specified time and temperature conditions. The rate of the rearrangement decreased from methyl isoatoate to *t*-butyl isoatoate. (Because of the unidentified product mixture, it is not known whether *t*-butyl isoatoate undergoes rearrangement or a decomposition reaction.) The rearrangement reaction was shown to be both metal (copper and iron) and base (triethylamine) catalyzed as rearrangements done in the presence of these materials were faster than in their absence. The rearrangement is apparently affected by the ionizing power of the solvent as the rate of rearrangement decreases in the following order DMSO > MeOH > *t*-BuOH > diglyme >> chloroform. This reaction also appeared to be dependent on the isoatoate concentration as the rate of rearrangement appeared to increase with increasing isoatoate concentration. Isoatoic anhydride may be an intermediate in the rearrangement reaction as it was one of the products isolated when diglyme was used as solvent. Both *N*-methyl and 5-chloroisoatoates rearrange faster than unsubstituted isoatoates.



Isoatoates also undergo another high temperature reaction, a relatively fast alcohol exchange. This exchange reaction is much faster than the rearrangement reaction as isopropyl isoatoate can be readily prepared from methyl isoatoate before any detectable rearrangement has taken place. Methyl isoatoate can also be readily made from



isopropyl isoatoate. *t*-Butyl isoatoate can be prepared from methyl isoatoate but its rate of formation is very slow.

The uncatalyzed ring opening of isoatoic anhydride is believed to occur by the reaction scheme proposed in Figure 1. Pathway one is a modification of a reaction scheme proposed by Bunnett and Naff (4) for the ring opening of isoatoic anhydride with amines. The products of the ring opening are explained by two competing reaction pathways. Pathway one involves the ionization and ring opening of 1 to form 2-carboxyphenyl isocyanate as a reactive intermediate. Alcohol then adds to the isocyanate group forming an isoatoate. The decrease in the rate of isoatoate formation with increasing bulk of the alcohol (the variation in ionizing power of the solvent is not considered here) correlates roughly with the known rate decrease observed for the addition of alcohols (5) to phenyl isocyanates (relative rate: *t*-Bu, 1; *i*-Pr, 30; Me, 26).

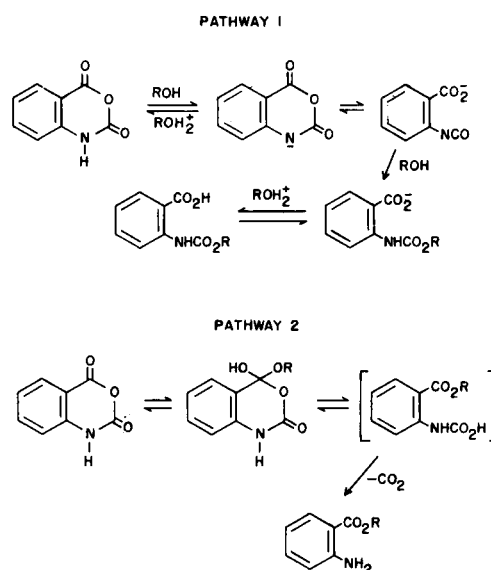


Figure 1. Proposed isoatoic anhydride ring opening pathways.

Pathway two involves the direct addition of alcohol to the carbonyl adjacent to the aromatic ring of 1 (addition of alcohol to the carbonyl adjacent to the nitrogen atom is electronically less favorable (9) followed by ring opening and loss of carbon dioxide to form the corresponding anthranilate. Due to the tetrahedral half acetal intermediate this pathway will be very susceptible to steric hindrance in the attacking alcohol. Thus pathway two should be most important for primary alcohols.

The observations concerning the preparation of isoatoates generally support the proposed reaction pathways. Two observations in particular support the proposed two pathway reaction scheme. *N*-Methylisoatoic anhydride reacts with isopropanol giving only isopropyl *N*-methylanthranilate. *N*-Methylisoatoic anhydride cannot ring open to an isocyanate intermediate thereby blocking any reaction by pathway one and making pathway two the only one available for ring opening. An expected ring opening by pathway two is slower as noted by the *N*-methylisoatoic anhydride reaction. This reaction had only gone to about 50% completion at a temperature 20° higher than for the unsubstituted 1. Additional support for competing pathway two is gained from the 30% yield of methyl anthranilate obtained in the preparation of methyl isoatoate. This yield of anthranilate is much higher than is obtained when methyl isoatoate is subjected to rearrangement reaction conditions for six hours. (Compare data in Table I with Table IV.)

There are at least two probable reaction schemes for the rearrangement reaction, an isocyanate-alcohol elimination-readdition reaction scheme (thermal elimination of alcohol from a carbamate (6) is well known) or by an internal displacement reaction (7). The previously re-

ported observations tend to support the mechanism outlined in Figure 2, an internal displacement mechanism very similar so that of Hegarty (7) proposed for the hydrolysis of phenyl isoatoate. An ionization step is supported by the observed metal and base catalysis. Both of these materials promote ionization of the acid group. Additional support for ionization being part of the rate determining process lies in the observed solvent effect and effect of ring substitution. Polar solvents such as dimethylsulfoxide promote the rearrangement while in a nonpolar solvent such as chloroform the reaction was not observed under the conditions tried. The 5-chloroisoatoate rearranged faster as an electron withdrawing substituent *meta* to a

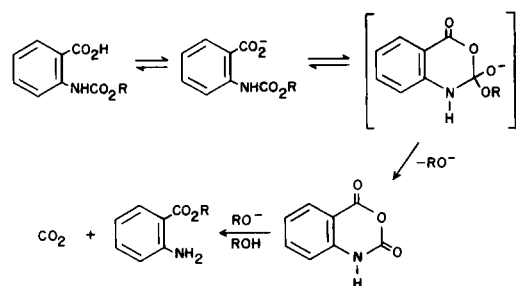


Figure 2. Proposed isoatoate rearrangement pathway.

carboxy group promotes its ionization. Support for the internal displacement by the *ortho* carboxy anion on the carbamate group rather than the alternate elimination mechanism is also given by the fact that *N*-methylisoatoates readily undergo the rearrangement reaction. The presence of a methyl substituent prevents alcohol elimination from the carbamate group. The last step of the reaction scheme is a relatively fast addition of alkoxide to the carbonyl adjacent to the aromatic ring of **1** opening the anhydride ring and forming the anthranilate product.

This study has shown that a wide variety of isoatoates can be prepared in moderate to good yield by the high temperature reaction of isoatoic anhydride with alcohols. This method is a good alternative to the current preparation of isoatoates synthesized by the reaction of the appropriate chloroformate with anthranilic acid (8). Isoatoates were shown to undergo two interesting high temperature reactions, an alcohol exchange and a rearrangement to anthranilates. Reaction schemes for the ring opening reaction and the rearrangement reaction were proposed.

EXPERIMENTAL

Chemicals.

Isoatoic anhydride (Sherwin-Williams Chemicals recrystallized); *N*-methylisoatoic anhydride, 5-chloroisoatoic anhydride and 5-nitroisoatoic anhydride, Sherwin-Williams Chemicals. Reagent, anhydrous solvents were also used.

Instruments.

Varian T-60 NMR; Perkin-Elmer 237 and 567 IR spectrometers; 300 and 1000 ml. Autoclave Engineers autoclave; 500 ml. bomb reactor; Thomas Hoover capillary melting point apparatus.

Preparation of Isopropyl Isoatoate.

To a 300 ml. autoclave was added 8.2 g. (0.05 mole) of isoatoic anhydride and 100 ml. of isopropyl alcohol forming a white suspension. The reactor was sealed, heated to 150-155° (20-30 minute heat-up time) and held at 152° for one hour with stirring. The reactor was cooled to room temperature and the yellow solution was removed by suction. After washing the walls of the reactor with 2-propanol the combined liquids were filtered to remove small amounts of insoluble material. The filtrate was reduced to dryness on a rotary film evaporator and the resulting solid oven dried. There was collected 10.7 g. of yellow-white solid (95% yield) which was identified by an infrared spectrum as being crude isopropyl isoatoate.

Other isoatoates prepared with alcohols boiling under 95° were synthesized in an autoclave as described above. For alcohols boiling over 95° the isoatoates were prepared in standard glassware under a nitrogen atmosphere. For relatively high boiling alcohols (boiling over 150°) the excess alcohol used in the preparation was removed using a vacuum pump.

Preparation of Methyl *N*-Methylisoatoate.

N-Methylanthranilic acid, 6.0 g. (0.04 mole) (prepared by hydrolysis of *N*-methylisoatoic anhydride) was mixed with 50 ml. of benzene and 5.6 ml. (0.039 mole) of triethylamine forming a solution. Then 4.0 g. (0.043 mole) of methyl chloroformate was added, with stirring, over a five minute period producing a white precipitate and a 20° temperature increase. After addition was complete the reaction mixture was filtered and the residue (triethylammonium chloride) washed with benzene. On cooling a solid precipitated from the benzene filtrate. This solid was collected and dried giving 5.0 g. (60% yield) of white solid shown by infrared and nmr spectra to be impure title isoatoate. The ammonium salt impurity was removed by dissolution in aqueous base and reprecipitation with aqueous acid.

Isopropyl *N*-methylisoatoates were prepared in a like manner.

Purification and Recrystallization of Isoatoates.

Isoatoates were purified by dissolving them in a slight excess of aqueous base, filtered to remove any insoluble material and then extracted with 2 or 3 portions of methylene chloride to remove emulsified anthranilate and other base insoluble impurities. The aqueous portion containing isoatoate was then carbon treated, filtered, precipitated with aqueous acid, filtered, washed with water and air dried. The lower alkyl isoatoates were recrystallized from alcohol-water yielding white crystalline solids. Due to an oiling out problem the longer chain alkyl isoatoates were recrystallized from chloroform-hexane or from hexane.

An alternate purification procedure was also used which worked well to remove base soluble impurities or color bodies. A concentrated (about 10-30% by weight) solution of isoatoate in aqueous base was prepared, filtered to remove insolubles, extracted 2-3 times with methylene chloride and then 10-20 g. of sodium chloride per 100 ml. of isoatoate solution was added soon precipitating a white solid. This white solid was collected, washed with cold aqueous saturated sodium chloride solution and cold water and dried. There was recovered about 80% of a material identified by nmr and infrared spectra as the sodium isoatoates. Isoatoate of reasonable purity could be obtained by redissolving, acidification and then recrystallization. This procedure worked best with ethyl and isopropyl isoatoates.

Rearrangement Reactions.

A solution of recrystallized methyl isatoate, 1.95 g. (0.01 mole) in 20 ml. of anhydrous methanol, was sealed into a 200 mm glass tube. The sealed tube was placed in a bomb along with a methanol heat transfer agent and the bomb was placed in an oil bath. The oil bath was heated to 160° (about one hour heat-up) and held at this temperature for six hours. After cooling the sealed tube was opened and the orange-pink solution was reduced to dryness on a rotary film evaporator. An nmr spectrum showed the crude reaction product to be 85% methyl isatoate and 15% methyl anthranilate.

The same general procedure was used for doing the other rearrangements listed in Table IV. For reactions involving catalysts, on the above scale, 0.1 ml. of triethylamine or a few strands of shredded copper were used.

Acknowledgments.

I would like to thank J. W. Long for suggesting this research project, L. Vacek for many helpful discussions and G. C. Sanzenbacher for collecting and interpreting the spectral data.

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(9) Because conclusive proof to the contrary has not been presented a referee has suggested that a nitrogen carbonyl half acetal intermediate is a reasonable alternative to the proposed pathway one. Since an *N*-methyl substituent usually increases, not decreases, the rate of addition to an adjacent carbonyl (7b), the observation that no isatoate was obtained when reacting alcohol with *N*-methylisatoic anhydride would seem to preclude a nitrogen carbonyl addition pathway.