Use of Acetyl Chloride–Triethylamine and Acetic Anhydride–Triethylamine Mixtures in the Synthesis of Isomaleimides from Maleamic Acids

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Procedures for preparing N-substituted isomaleimides by reacting N-substituted maleamic acids with acetyl chloride–triethylamine and acetic anhydride–triethylamine mixtures are described. In contrast to reports by others, isomaleimides can be prepared in good yield with these reagents, provided reaction conditions are carefully controlled. The influence of temperature, amine concentration, dehydrating agent, and solvent on the preparation of *N*-(*n*-propyl)isomaleimide, *N*-(*n*-butyl)isomaleimide, *N*-(*sec*-butyl)isomaleimide, *N*-(*tert*-butyl)-isomaleimide, and *N*-phenylisomaleimide was investigated. At least 2 mol of amine per mol of maleamic acid should be used to obtain good yields of most *N*-alkylisomaleimides, but no more than 1 mol of amine per mol of maleamic acid should be used when *N*-arylisomaleimides are prepared. A mechanism is proposed to rationalize these results.

A number of papers[1-10] have appeared recently which describe the preparation and reactions of N-substituted isomaleimides, bis(isomaleimides), and cyclic isoimidium salts. These materials are generally prepared by dehydration of maleamic acids under kinetically controlled conditions. They often rearrange in the presence of catalytic amounts of base at elevated temperatures to form the N-substituted maleimides, which are usually the thermodynamically more stable isomers.

Trifluoroacetic anhydride, ethyl chloroformate, and *N*,*N*′-dicyclohexylcarbodiimide are the reagents currently favored for use in dehydrating maleamic acids to obtain isomaleimides; their high reactivity favors the formation of kinetically controlled products, and the relatively weak bases which result as by-products from these reagents are not efficient catalysts for isoimide isomerization. Acetyl chloride and acetic anhydride have also been used in isomaleimide preparations,[6] but some workers[2,3] have suggested that these reagents are not satisfactory for this purpose. It seems that reaction conditions have a significant influence on the nature of the products obtained from reactions involving these reagents.

The purpose of the present paper is to show that acetyl chloride or acetic anhydride can be used to prepare isomaleimides and related compounds in high yield and good purity, provided that reaction conditions are controlled carefully. We have found that acetyl chloride–triethylamine under the appropriate conditions behaves just like trifluoroacetic anhydride in producing isomaleimides from corresponding maleamic acids.

Cotter, *et al.*,[3] reported that the reactions of *N*-(*n*-butyl)maleamic acid with acetic anhydride–triethylamine or acetyl chloride–triethylamine mixtures yielded *N*-(*n*-butyl)maleimide. When we repeated these reactions, the principal product was *N*-(*n*-butyl)isomaleimide. When this material was refluxed (100°) for 3 hr and then redistilled, pure *N*-(*n*-butyl)maleimide was obtained. It appears that Cotter and coworkers[3] obtained *N*-(*n*-butyl)isomaleimide as the major initial product but that it rearranged to *N*-(*n*-butyl)maleimide under their work-up conditions.

The reaction of *N*-(*n*-butyl)maleamic acid at −20° with acetyl chloride–triethylamine in methylene chloride gave almost pure (97%) *N*-(*n*-butyl)isomaleimide in 61% yield. This result was comparable to that obtained in the reaction of the maleamic acid with trifluoroacetic anhydride–triethylamine at 25°. The reactions of other *N*-alkylmaleamic acids with acetyl chloride–triethylamine or acetic anhydride–triethylamine mixtures also yielded isomaleimides in high purity and reasonable yield (Table I) when the reactions were conducted at low temperature with 2 mol of triethylamine per mol of maleamic acid. The use of smaller amounts of amine resulted in lower product yields, probably due to acid-catalyzed hydrolysis of isomaleimides during work-up.[3]

In most cases, the yields obtainable by this procedure were comparable to those obtained when trifluoroacetic anhydride was the dehydrating agent. The yields obtained in the preparation of *N*-(*sec*-butyl)isomaleimide and *N*-(*tert*-butyl)isomaleimide with acetyl chloride or acetic anhydride were less than were obtained with trifluoroacetic anhydride, but this difference is probably due to differences in the reactivities of the reagents and not to differences in selectivity; both *N*-(*sec*-butyl)isomaleimide and *N*-(*tert*-butyl)isomaleimide were stable to the reaction conditions employed. In fact, we failed to prepare *N*-(*tert*-butyl)maleimide and *N*-(*sec*-butyl)maleimide by the general method of heating the maleamic acids in excess acetic anhydride–sodium acetate. These maleimides could only be obtained in low yields (2%) by fusing the amic acids for 0.5 hr, followed by distillation.[11,12] It seems that sterically hindered isomaleimides are difficult to rearrange to isoimides.

The reaction of *N*-phenylmaleamic acid with acetyl chloride in the presence of 1 equiv of triethylamine at −22° yielded *N*-phenylisomaleimide in 63% yield. The recrystallized product did not absorb at ~1730

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TABLE I

RESULTS OF REACTION OF SOME *N*-ALKYLMALEAMIC ACIDS WITH ACETIC ANHYDRIDE, ACETYL CHLORIDE, OR TRIFLUOROACETIC ANHYDRIDE IN THE PRESENCE OF TRIETHYLAMINE[a]

Maleamic acid	Dehydrating agent	*T*, °C	Time, hr	Overall yield, %	Composition of product % imide	 % isoimide
N-(*n*-Propyl)maleamic acid	CH_3COCl	−20	1	61	3	97
	$(CF_3CO)_2O$	25	0.5	65		100
N-(*n*-Butyl)maleamic acid	CH_3COCl	5	16	40	17	83
	CH_3COCl	−20	1	61	3	97
	Ac_2O	5	3	38	20	80
	$(CF_3CO)_2O$	25	0.5	62		100
N-(*sec*-Butyl)maleamic acid	CH_3COCl	0	1	25	Trace	$\sim$100
	$(CF_3CO)_2O$	25	1	48		100
N-(*tert*-Butyl)maleamic acid	CH_3COCl	25	5	32	Trace	$\sim$100
	CH_3COCl	−15	5	31	Trace	$\sim$100
	Ac_2O	60	1	31	Trace	$\sim$100
	Ac_2O	−15	5	31	Trace	$\sim$100
	$(CF_3CO)_2O$	25	5	47		100
1,2-Bis(3-carboxyacrylyl) hydrazine	CH_3COCl	25	3	50		100
	$(CF_3CO)_2O$[b]	Reflux	5	60		100

[a] Two equivalents of triethylamine was used in each experiment. [b] Imide was detected by hydrolysis of product, followed by infrared spectroscopic examination of a CCl_4 extract of the hydrolysate.

TABLE II

PRODUCTS OBTAINED FROM THE REACTION OF *N*-PHENYLMALEAMIC ACID WITH ACETYL CHLORIDE–TRIETHYLAMINE UNDER VARIOUS CONDITIONS

Temp, °C	Solvent	Mol Et_3N/mol acid	Time, hr	Overall yield, %	Composition of product[a] % imide	 % isoimide
−22	CH_2Cl_2	1	1	63		100
−20	$CHCl_3$	2	1	62	99	Trace
25	CH_2Cl_2	1	1	60	77	23
25	CH_2Cl_2	2	1	60	92	8
38	C_6H_6	1	1	55	68	32
38	C_6H_6	2	1	51	99	Trace
80	C_6H_6	1	2	40	100	

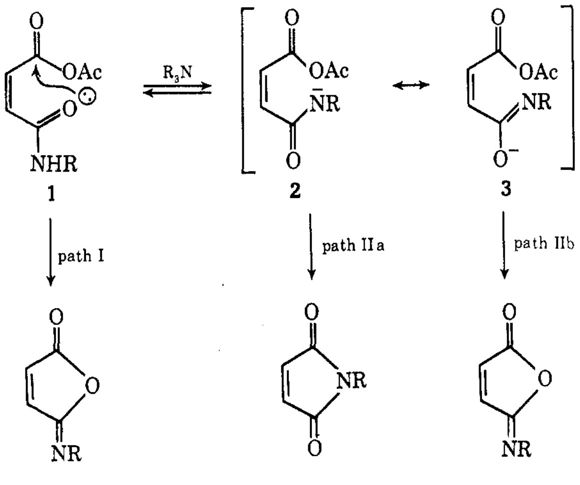
[a] Product compositions were determined by infrared analysis of product mixtures in CCl_4. The relative intensities of the carbonyl absorptions of both isomers were easily measured.

cm^{-1}, indicating that no *N*-phenylmaleimide was present. Use of 2 equiv of triethylamine caused *N*-phenylmaleimide to be the major product of the reaction. This result is interesting because *N*-phenylisomaleimide did not rearrange to the imide during a 6-hr treatment with either triethylamine or a triethylamine–acetic acid mixture. High temperatures also favored the formation of *N*-phenylmaleimide. The results of these studies are summarized in Table II.

Our results indicate that the *N*-phenylmaleimide formed with acetyl chloride–triethylamine mixtures at or below room temperature is derived from *N*-phenylmaleamic acid and not from *N*-phenylisomaleimide. Kinetic evidence for a direct route to *N*-arylmaleimides in acetic anhydride–sodium acetate dehydration systems[8,13] has also been published. Unfortunately, rearrangement of isoimides to imides is a competing reaction in the acetic anhydride–sodium acetate systems. Since this does not seem to be the case in the acetyl chloride–triethylamine system, this system can probably be used to investigate the mechanism of the direct conversion of *N*-arylmaleamic acids to *N*-arylmaleimides.

The role of amine concentration on the course taken by maleamic acid dehydrations with acetyl chloride–triethylamine mixtures can be rationalized in terms of the general mechanism for amic acid dehydrations that has evolved[7,8,14] during the last ten years. The first step in these reactions might be envisioned (Scheme I) as the formation of the mixed anhydride 1 by reaction of the maleamic acid with acetyl chloride or acetic anhydride. The subsequent cyclization step could involve either the carbonyl oxygen atom or the amide nitrogen atom. The former would be expected to be the more reactive in relatively neutral media (path I), so that isomale-

SCHEME I



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imides would be the favored products. However, in media of higher basicity, or presumably also at high temperature, the amide ion might form and this could then participate in cyclization reactions which lead either to the isoimide or the imide (path II).

The path taken by the reaction will depend on the position of the equilibrium between the neutral intermediate **1** and its ion (**2** + **3**) and also on the relative electron densities of the oxygen and nitrogen atoms in the ion (**2** + **3**). When *N*-alkylmaleamic acids are used, the equilibrium would tend to form the neutral intermediate and this would be most likely to form the isoimide. When substituents capable of stabilizing the amide ion, such as phenyl groups, are present, the ion may be present in appreciable amount, especially at high amine concentration. In this case, the imide can form in addition to the isoimide. The ion (**2** + **3**) can yield either imide or isoimide depending on whether the cyclization step involves the carbonyl oxygen or the amide nitrogen. This may depend to a certain extent on the relative electron densities of the two atoms in a particular compound. When electron-releasing substituents (*e.g.*, alkyl) are present on the nitrogen atom, a high electron density on the carbonyl oxygen might be anticipated, and this would favor the formation of isoimide (path IIb). When electron-withdrawing substituents (*e.g.*, phenyl) are present, the electron density on the oxygen atom may be reduced to such an extent that imide formation may be favored (path IIa).[15]

A complete analysis of the mechanism should give consideration to stabilities, reactivities, and rates of interconversion of the various conformers of the amide and its ion, but such consideration is inappropriate at the present time.

Experimental Section

Preparation of Maleamic Acids.—With the exception of 1,2-bis(3-carboxyacrylyl)hydrazine,[6] all N-substituted maleamic acids were prepared according to the method of Liwschitz, *et al.*[16] They were purified by dissolution in dilute $NaHCO_3$, followed by precipitation with HCl, washing with cold water, and drying. Their melting points agreed with literature values. New materials prepared were *N*-(*sec*-butyl)maleamic acid [mp 87° (*Anal.* Calcd for $C_8H_{13}NO_3$: C, 56.14; H, 7.60; N, 8.18. Found: C, 56.30; H, 7.65; N, 8.03)], and *N*-(*tert*-butyl)maleamic acid [mp 157–158° (*Anal.* Calcd for $C_8H_{13}NO_3$: C, 56.14; H, 7.60; N, 8.18. Found: C, 56.34; H, 7.62; N, 8.11)].

General Procedure for the Preparation of Isomaleimides Using Acetyl Chloride or Acetic Anhydride.—A solution of the maleamic acid (0.1 mol) and triethylamine (0.2 mol) in methylene chloride (200 ml) was cooled to the desired temperature. Acetyl chloride or acetic anhydride (0.1 mol) was added dropwise with stirring. The temperature was kept constant during the addition and also after that for a certain time. This was followed by filtration and treatment of the filtrate with either dilute sodium bicarbonate or dilute sodium hydroxide solution. When bicarbonate was added, the solution had to stand from 0.5–2 hr. This caused loss of some *N*-alkylisomaleimides since they are sensitive to water and hydrolyze slowly. The best procedure was to simply treat the product with the stoichiometric amount of dilute sodium hydroxide. The methylene chloride layer was separated, washed, and dried. The solvent was then removed under reduced pressure and the residue was distilled under reduced pressure or recrystallized, depending on whether it was liquid or solid. This procedure worked satisfactorily for the following compounds: *N*-(*n*-propyl)isomaleimide [bp 59° (2 mm) (*Anal.* Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.47; N, 10.07. Found: C, 60.20; H, 6.18; N, 9.96)]; *N*-(*n*-butyl)isomaleimide [bp 62° (1 mm)]; *N*-(*sec*-butyl)isomaleimide [bp 60° (1 mm) (*Anal.* Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.25; H, 7.59; N, 8.91)]; *N*-(*tert*-butyl)isomaleimide [bp 45° (0.5 mm) (*Anal.* Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.45; H, 7.12; N, 9.00)]; and *N*-phenylisomaleimide[17] (mp 61°). The yields are given in Tables I and II.

N,*N*′-biisomaleimide was also prepared by the above procedure. It was insoluble in methylene chloride so the solids formed in the reaction were collected, washed successively with water, dilute $NaHCO_3$, and water, and then dried. Recrystallization from DMF yielded pure material, mp 26°.

Preparation of Isomaleimides Using Trifluoroacetic Anhydride–Triethylamine.—The procedure of Cotter, *et al.*,[3] was followed to prepare *N*-phenylisomaleimide, *N*-(*n*-propyl)isomaleimide, *N*-(*n*-butyl)isomaleimide, *N*-(*sec*-butyl)isomaleimide, and *N*-(*tert*-butyl)isomaleimide for comparison purposes. The compounds obtained were identical (ir, nmr, vpc) with the products obtained when acetyl chloride or acetic anhydride was used in the presence of triethylamine.

Analysis of Product Mixtures.—In these studies, traces of imides in the isoimides were determined by reacting the products with dilute acid. This treatment caused the isoimides to be hydrolyzed, but the imides were not affected. The imide (if present) was extracted with carbon tetrachloride and detected by infrared spectroscopy.

Product compositions were also determined by ir and nmr analyses. The carbonyl groups in the isomaleimides absorbed at 1800 cm^{-1}, and their vinylic protons were observed (CCl_4) as an AB pattern (J = 6 cps) centered at 6.8–7.1 ppm, whereas the imide carbonyls absorbed at 1680–1730 cm^{-1} and the imides showed a singlet olefinic resonance at 6.5–6.8 ppm.

Isomerization of *N*-Substituted Isomaleimides.—*N*-Phenylisomaleimide, *N*-(*n*-propyl)isomaleimide, and *N*-(*n*-butyl)isomaleimide were isomerized with sodium acetate–acetic acid[3] to obtain the corresponding imides. *N*-(*n*-Propyl)isomaleimide and *N*-(*n*-butyl)isomaleimide were also isomerized by vigorous heating. However, *N*-phenylisomaleimide, *N*-(*sec*-butyl)isomaleimide, and *N*-(*tert*-butyl)isomaleimide could not be rearranged to the corresponding imides by heat. Furthermore, *N*-(*sec*-butyl)isoimide and *N*-(*tert*-butyl)isomaleimide were unchanged after being refluxed for 1 hr with a mixture of NaOAc and benzene.

Treatment of *N*-Phenylisomaleimide with Triethylamine or a Triethylamine-Acetic Acid Mixture.—A mixture of pure *N*-phenylisomaleimide (1 g, 0.006 mol), benzene (35 ml), and triethylamine (0.1 g, 0.001 mol) was stirred at room temperature for 6 hr. A portion of the mixture ws then evaporated to dryness under reduced pressure. The melting point (61°) and infrared spectrum of the residue showed it to be essentially pure *N*-phenylisomaleimide. A similar experiment in which equimolar amounts of triethylamine and acetic acid were present also failed to cause isomerization.

Registry No.—Acetyl chloride, 75-36-5; triethylamine, 121-44-8; acetic anhydride, 108-24-7; *N*-(*sec*-butyl)maleamic acid, 27396-37-8; *N*-(*n*-propyl)isomaleimide, 27396-38-9; *N*-(*n*-butyl)isomaleimide, 27396-39-0; *N*-(*sec*-butyl)isomaleimide, 27396-40-3; *N*-(*tert*-butyl)isomaleimide, 27396-41-4; *N*-phenylisomaleimide, 19990-26-2; *N*,*N*′-biisomaleimide, 6990-21-2.

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[15] It is interesting to report at this point that the reaction of *N*-(*o*-nitrophenyl)maleamic acid with 1:1 acetyl chloride–triethylamine in methylene chloride at −15° yielded a mixture of imide and isoimide.

[16] Y. Liwschitz, Y. E. Pfeffermann, and Y. Lapidoth, *J. Amer. Chem. Soc.*, **78**, 3069 (1956).

[17] In the preparation of *N*-phenylisomaleimide, unreacted phenylmaleamic acid precipitated when water was added to the filtrate. One crystallization of the crude product from supercooled CCl_4 gave pure *N*-phenylisomaleimide.