Aminimides. II. A one-step synthesis of aminimides from carboxylic acid esters[1]

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The general applicability of preparing aminimides from esters and *in situ* generated 1,1,1-trimethylaminimine is reported. Acyclic, alicyclic, aromatic, and heteroaromatic trimethylaminimides have been synthesized by the one-step reaction. The synthetic scheme consists of reacting an ester with a 1,1,1-trimethylhydrazinium salt in the presence of an anhydrous base such as sodium methoxide. The choice of solvent, reaction temperature, and base and the electronegativity of the acyl substituent influence the ease of aminimide formation.

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The preparation of aminimides by the route outlined in eq. [1] has previously been reported by three different laboratories (1–3). The method used in each case involved three steps, starting with the acyl halide. The intermediate hydrazide may be obtained from esters and 1,1-dimethylhydrazine only if the ester possesses strongly electron withdrawing groups, such as cyano, nitro, or halo, in the α position. With unsubstituted aliphatic or aromatic esters, the nucleophilicity of 1,1-dimethylhydrazine is not sufficient to displace the alkoxy anion, and little or no hydrazide is obtained

$$[1]\quad \underset{\text{O}}{\overset{\|}{\text{RCCl}}} + \text{H}_2\text{NN(CH}_3)_2 \xrightarrow{-\text{HCl}} \underset{\text{O}}{\overset{\|}{\text{RCNHN(CH}_3)_2}} \xrightarrow{\text{CH}_3\text{X}} \underset{\text{O}}{\overset{\|}{\text{RCNHN}}}\overset{\oplus}{\text{(CH}_3)_3}\text{X}^{\ominus} \xrightarrow[-\text{HX}]{\text{NaOH,}} \underset{\text{O}}{\overset{\|}{\text{RCNN}}}\overset{\ominus\oplus}{\text{(CH}_3)_3}$$

X = Cl, I, or OTs

(4). Thus, the general preparation of aminimides has been limited to the use of the less available acid halide or anhydride.

In connection with a continuing study on the chemistry of aminimides, we have investigated methods of preparing aminimides directly from esters and 1,1,1-trimethylaminine (5). While our work was in progress, Schiessl and Appel reported the synthesis of *N*-dimethylanilinophenylpropiolimide (I) by the reaction of *N*,*N*-dimethyl-*N*-phenylaminimine, generated *in situ*, with ethyl phenylpropiolate (6). The work reported in this paper demonstrates the general applicability of this reaction, as well as improvements in the experimental procedure.

$$\text{PhC}{\equiv}\text{C}\underset{\text{O}}{\overset{\|}{\text{C}}}\text{NN}\overset{\ominus\oplus}{\text{(CH}_3)_2}\text{Ph}$$

I

[1]For part I in this series, see ref. 3.

RESULTS

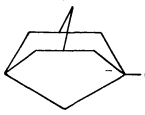
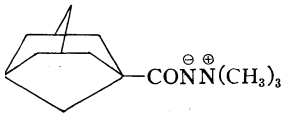
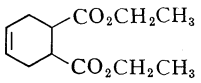
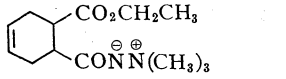
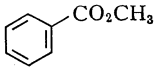
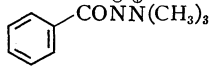
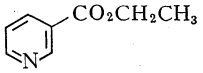
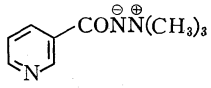
Trimethylaminimides were prepared by reacting esters with 1,1,1-trimethylhydrazinium salts in the presence of an anhydrous base. Polar solvents and moderate temperatures were used. Little difference was found between the 1,1,1-trimethylhydrazinium salts. However, of several bases studied, including triethylamine, sodium hydroxide, sodium isopropoxide, sodium *t*-butoxide, and sodium methoxide, sodium methoxide gave the highest yields (Table I). Numerous polar solvents, such as acetonitrile, triethylamine, *N*,*N*-dimethylformamide, dimethyl sulfoxide, isopropanol, and *t*-butanol, as well as the comparatively nonpolar solvent benzene, were used. *t*-Butanol gave the highest yields with the fewest by-products. Although higher yields were obtained in refluxing *t*-butanol, cleaner products were obtained at more moderate temperatures. With trimethylamine methacrylimide (7)

TABLE I

Varying conditions for synthesis of trimethylamine methacrylimide (7)

Trimethylhydrazinium salt	Base	Solvent	Temperature (°C)	Time (h)	Crude yield of aminimide (%)
Tosylate	$NaOCH_3$	CH_3CN	Reflux	3	7
Tosylate	$NaOCH_3$	*t*-Butanol	Reflux	3	63
Chloride	$NaOCH_3$	*t*-Butanol	Reflux	3	58
Chloride	$NaOCH_3$	*t*-Butanol	Reflux	6	91
Chloride	KO-*t*-Bu	*t*-Butanol	Reflux	6	85
Chloride	$NaOCH_3$	$(CH_3CH_2)_3N$	Reflux	13	52
Chloride	$NaOCH_3$	*N,N*-Dimethylformamide	84	7	<5
Chloride	$NaOCH_3$	Dimethyl sulfoxide	84	6	<5
Chloride	$(CH_3CH_2)_3N$	$(CH_3CH_2)_3N$	Reflux	9	None
Chloride	$NaOCH_3$	*t*-Butanol	48	4	78
Chloride	$NaOCH_3$	Isopropanol	48	4	68
Chloride	NaO-*i*-P	Isopropanol	45	6	43
Chloride	NaOH	Benzene–water azeotrope	Reflux	20	9

TABLE II

Ester	Trimethylhydrazinium salt	Temperature (°C)	Time (h)	Aminimide	Crude yield (%)
$CH_3(CH_2)_{10}CO_2CH_2CH_3$	Chloride	79	4	$CH_3(CH_2)_{10}CO\overset{\ominus\oplus}{N}N(CH_3)_3$ Trimethylamine laurimide	95
 (8)	Tosylate	70	4	 Trimethylamine adamantane-1-carboximide	63.6
	Chloride	48	48	 Trimethylamine carboximidyl-2-carbethoxycyclohex-4-ene	63
	Chloride	82	3	 Trimethylamine benzimide*	90.3
	Chloride	45	3½	 Trimethylamine nicotinimide	94
$CF_3CF_2CO_2CH_2CH_3$	Chloride	55	½	$CF_3CF_2CO\overset{\ominus\oplus}{N}N(CH_3)_3$ Trimethylamine perfluoropropionimide†	Quantitative

*Carried out in acetonitrile; see refs. 1 and 2.
†Made by R. Virkhaus.

reaction was rapid initially, even at room temperature.

Table II lists the various aminimides synthesized and their corresponding starting esters. In all cases sodium methoxide was used; the solvent was *t*-butanol, except where noted. In most cases the reaction proceeded with ease and the yield was high.

Esters with electron-withdrawing substitutents, such as aromatic or perfluoro groups seemed to undergo displacement more easily than unsubstituted aliphatic esters. The progress of the reaction was followed by observing the decrease in basicity. Completion of reaction was observed at essentially a pH of 7. Removal of the sodium chloride by filtration and evaporation of the solvent yielded crude aminimide. The aminimides were identified by their infrared and nuclear magnetic resonance (n.m.r.) spectra and by their elemental analysis. In selected instances the aminimides were pyrolyzed to isocyanates (1–3), which were also characterized.

DISCUSSION

It is presumed that the reaction proceeds via the formation of the intermediate reactive nucleophile 1,1,1-trimethylaminimine (II), which, in turn, displaces the alkoxide from the ester (eq. [2]). 1,1,1-Trimethylaminimine was first suggested by Wittig and Rieber (*5a*), who obtained a precipitate when a solution of phenyllithium in ether was added to trimethylhydrazinium iodide; however, no identification was attempted.

The existence of this uncharacterized intermediate was revealed in a German patent (*5b*); it was reported to be an unstable solid, m.p. 58–60°. A much more detailed paper on the isolation, characterization, and evaluation of 1,1,1-trimethylaminimine was recently published while our work was being completed (*5c*). The authors were able, in this case, to isolate the adduct formed between 1,1,1-trimethylaminimine and 2 moles of *t*-butanol, which was found to be more heat stable (to 88°) and much more stable to polar solvents than the free aminimine II. This no doubt is the reason why our syntheses have proceeded so much more easily in *t*-butanol than in other polar solvents, and also why we have observed cleaner reaction products at lower temperatures.

Schiessl and Appel (6) recently reported the use of tetrahydrofuran as the solvent in the *in situ* syntheses of *N*-dimethylanilinophenylpropiolimide (I). In this case the reaction was carried out at room temperature, where the intermediate aminimine would be stable. However, a long reaction time seemed to be necessary. To reduce the reaction time, elevated temperatures are

$$[2]\quad H_2\overset{\oplus}{N}\overset{\ominus}{N}(CH_3)_3X^{\ominus} + CH_3ONa \xrightarrow[-NaX]{-CH_3OH,} \underset{\text{II}}{H\overset{\ominus\oplus}{N}N(CH_3)_3} \xrightarrow{RCO_2CH_3} RC(=O)\overset{\ominus\oplus}{N}N(CH_3)_3 + CH_3OH$$

X = Cl or OTs

probably needed, in which case decomposition of the imine should occur. The use of *t*-butanol seems to alleviate such a problem.

EXPERIMENTAL

The melting points are corrected. The infrared spectra were obtained on a Perkin–Elmer 237B grating spectrophotometer, and the n.m.r. spectra (τ scale) on a Varian A-60A spectrometer with tetramethylsilane as an internal standard. The elemental analyses were perfomed either by Huffman Laboratories, Inc., Wheatbridge, Colorado, or by Mr. Clifford Glowacki of these laboratories on an F & M carbon, hydrogen, and nitrogen analyzer, model 185.

General Procedure for Synthesis of Aminimides

Equimolar amounts (0.1 mole) of the ester, the 1,1,1-trimethylhydrazinium salt, and sodium methoxide were placed in 75 ml of dry solvent and, while being stirred vigorously, were heated for the period of time indicated in Table II. While still warm, the reaction mixture was filtered and the filtrate then evaporated *in vacuo* to give the crude aminimide.

Trimethylamine Laurimide

The crude product was isolated as above. Recrystallization from hexane gave white needles, m.p. 53–54°. The infrared spectrum (halocarbon mull) showed the expected absorption at 1 575 cm^{-1} (aminimide). Thermogravimetric analysis showed an onset decomposition temperature of 170°. The n.m.r. spectrum ($CDCl_3$) exhibited a singlet at 6.59 p.p.m. and multiplets from 7.7 to 9.0 p.p.m. (mainly at 8.72 p.p.m.) and at 9.12 p.p.m. in the expected ratio of 9:20:3, respectively.

Anal. Calcd. for $C_{15}H_{32}N_2O$: C, 70.25; H, 12.58; N, 10.92. Found: C, 70.32; H, 12.46; N, 11.02.

Trimethylamine Adamantane-1-carboximide

The crude product was isolated as above. Sublimation at 110° and 0.2 mm gave a white crystalline compound, m.p. 174–175°. The infrared spectrum (halocarbon mull) showed the aminimide absorption at 1 570 cm^{-1}, and no ester carbonyl band. The n.m.r. spectrum ($CDCl_3$) exhibited absorption at 8.29, 8.12, and 6.67 p.p.m. in a ratio (the two former to the last) of 15:9, as expected.

Anal. Calcd. for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.23; N, 11.86. Found: C, 71.28; H, 10.23; N, 11.86.

Thermogravimetric analysis showed the onset of decomposition at 180°. Pyrolysis of the aminimide above 180° gave the known isocyanate, m.p. 143–145° (lit. (9) m.p. 144–145°). The infrared spectrum (halocarbon mull) showed the expected band at 2 255 cm^{-1}.

About 50 mg of the isocyanate was dissolved in 3 ml of absolute methanol containing one drop of 1 *M* sodium hydroxide. The resulting mixture was refluxed for 15 min and then poured over ice. The resulting solid was removed by filtration and dried, m.p. 118–120° (lit. (9) m.p. 120°). The infrared spectrum (halocarbon mull) showed bands at 3 415, 3 275, 1 725, and 1 550 cm^{-1}, corresponding to a urethane structure.

Trimethylamine Carboximidyl-2-carbethoxycyclohex-4-ene

To a stirred solution of 22.6 g (0.1 mole) of diethyltetrahydro-Δ^4-phthalate and 22.1 g (0.2 mole) of trimethylhydrazinium chloride in 150 ml of dry *t*-butanol was added 10.8 g (0.2 mole) of sodium methoxide. The reaction mixture turned light yellow and warmed to 30°. The mixture was then heated at 48° for 48 h before it was filtered. Evaporation of the filtrate *in vacuo* gave a residue containing at least two components (as shown by thin-layer chromatography). Extraction with benzene left behind a material containing trimethylhydrazinium chloride and what is believed to be a small amount of the bisaminimide. Evaporation of the benzene layer gave 16 g of a viscous, pale-yellow oil. Chromatography over silica gel, with 2 parts of acetone and 1 part of methanol as eluent, gave a viscous oil showing only one component on thin-layer chromatography, n_D^{50} 1.4938. The infrared spectrum (smear) showed peaks at 3 025, 1 730, 1 655, and 1 580 cm^{-1}, as expected. We were unable to obtain a good elemental analysis of this viscous oil. However, the following chemical conversion into more easily purified materials gave proof of structure.

The aminimide (4 g) was pyrolyzed under vacuum. The decomposition took place at about 165° and gave 2.2 g of isocyanate, which distilled as a colorless oil. Redistillation gave the analytical sample, b.p. 90° at 1.5 mm, n_D^{26} 1.4724. The infrared spectrum (smear) showed significant peaks at 3 040, 2 270, 1 740, and 1 660 cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}NO_3$ (195.21): C, 61.52; H, 6.71. Found: C, 61.20; H, 6.80.

A few drops of the isocyanate were mixed with a large excess of anhydrous methanol and a drop of triethylamine and allowed to stand for 15 h at room temperature. Evaporation of the solvent gave a colorless oil, which was distilled, b.p. 122° at 0.15 mm, n_D^{26} 1.4843. The infrared spectrum (smear) exhibited significant peaks at 3 350, 3 030, 1 730, 1 660, and 1 530 cm^{-1}, confirming the urethane structure.

Anal. Calcd. for $C_{11}H_{17}NO_4$ (227.26): C, 58.13; H, 7.54. Found: C, 57.96; H, 7.58.

Trimethylamine Benzimide

The crude product was isolated as stated in the general procedure above. Recrystallization from chloroform–hexane gave a white crystalline product, whose mixture melting point with authentic trimethylamine benzimide (1, 2) was not depressed. The infrared spectra were identical.

Trimethylamine Nicotinimide

The crude product was isolated by the general procedure above. Several recrystallizations from benzene gave a white crsytalline solid, m.p. 110–112°. The infrared spectrum (Nujol mull) showed the expected band at 1 560 cm^{-1}, and no ester carbonyl band. The n.m.r. spectrum ($CDCl_3$) showed absorption at 6.54 (singlet), 2.81 (two doublets), 1.83 (two triplets), 1.49 (two doublets), and 0.92 (multiplet) p.p.m. in the expected area ratio of 9:1:1:1:1.

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.45. Found: C, 60.60; H, 7.23; N, 23.51.

Thermogravimetric analysis showed the onset of decomposition at 155°. Several grams of the aminimide were pyrolyzed at 180–230° and 20 mm. A pale-yellow solid formed in the condenser. This solid was chromatographed over silica gel, with methanol as eluent, to give a white solid, m.p. 318° (decomp.). The infrared spectrum (Nujol mull) showed peaks indicative of the isocyanurate at 3 030, 1 700 (split), 1 580, 1 480, 1 060, 805, 760, and 712 cm^{-1}.

Anal. Calcd. for $C_{18}H_{12}N_6O_3$: C, 60.00; H, 3.36; N, 23.33. Found: C, 59.94; H, 3.26; N, 23.59.

Trimethylamine Perfluoropropionimide

A quantitative yield of the crude product was obtained by the general procedure above. Chromatography on silica gel, with chloroform as eluent, gave a white crystalline compound, m.p. 104–107°. The infrared spectrum (halocarbon mull) showed the expected absorption at 1 659 cm^{-1} (aminimide). Thermogravimetric analysis showed the onset of decomposition at 150°.

Anal. Calcd. for $C_6H_9F_5N_2O$: C, 32.73; H, 4.12; N, 12.73. Found: C, 32.96; H, 4.27; N, 12.70.

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