

REACTION OF ALIPHATIC ISOCYANIDES WITH CHLOROACETIC ANHYDRIDE AND TRIFLUOROACETIC ANHYDRIDE

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Methyl isocyanide reacts with chloroacetic anhydride and trifluoroacetic anhydride while yielding derivatives of chloropyruvic and trifluoropyruvic acid methyl amides, *II* and *IV*. The reaction of tert-butyl isocyanide with the same acid anhydrides gives rise to unstable adducts which can be hydrolyzed to form derivatives of tartronic acid, *V*, *VIa* and *VIb*.

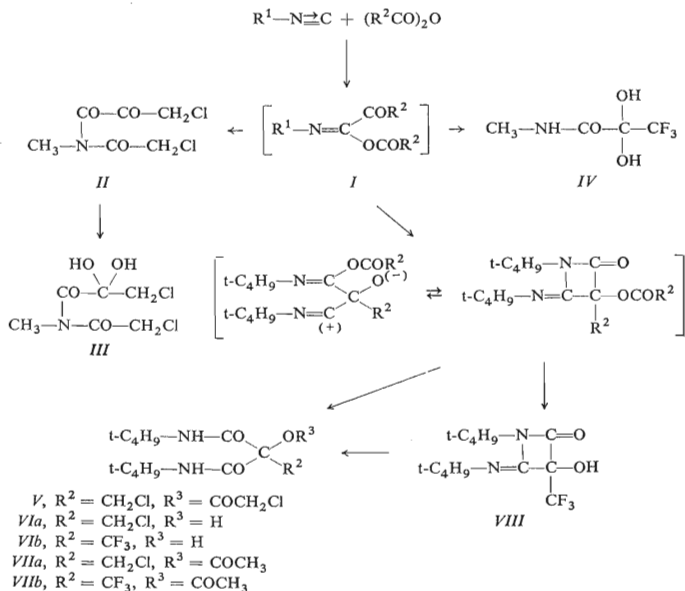
Isocyanides are known¹⁻⁴ to react with strong Lewis acids, such as *e.g.* BF_3 etherate. They also react with carboxylic acid chlorides⁵⁻⁷ or with the Vilsmeier-Haack reagent⁸. On the other hand, a reaction of isocyanide with carboxylic acid anhydride has not yet been described. It can be assumed therefore that isocyanides do not react with anhydrides of unsubstituted carboxylic acids, which has probably been attempted. This fact has been checked in preliminary experiments by following the IR spectra of solutions of mixtures of methyl isocyanide and acetic anhydride.

It seemed interesting to investigate a reaction of isocyanide with the carboxylic acid anhydride whose electron affinity is enhanced by substitution. We have chosen chloroacetic anhydride and trifluoroacetic anhydride; methyl isocyanide and tert-butyl isocyanide have been chosen as representatives of alkyl isocyanides. We have found out recently^{9,10} that tert-butyl isocyanide reacts with a protic acid (HCl) differently from other isocyanides. Therefore, a different course could be expected also in this case.

Methyl isocyanide yields with chloroacetic anhydride a 1 : 1 adduct, for which structure *I* could be foreseen similarly to the reaction products of isocyanides with acid chlorides. The IR spectrum of the adduct exhibits two carbonyl bands at 1705 and 1735 cm^{-1} . If the band with the lower frequency is assigned to the amide carbonyl group, the other band should be attributed to the carbonyl group of the ester or anhydride type. However, the wave number of this band is too low in this case. The wave numbers of the carbonyl bands of chloroacetic anhydride were 1800 and 1860 cm^{-1} , those of ethyl chloroacetate were 1735 and 1760 cm^{-1} ; N,N'-di(tert-butyl)-O-chloroacetyl-2-chloromethyltartronamide had its ester carbonyl group at 1770 cm^{-1} . It is likely that in our case compound *II* arises from the primarily formed adduct *I* by Mumm's rearrangement¹¹. In accordance with structure *II*, the latter compound readily gives hydrate *III*, in the IR spectrum of which the band

of the ketone carbonyl group at 1735 cm^{-1} is missing compared with the spectrum of compound *II*, and a broad band is observed at $3100\text{--}3500\text{ cm}^{-1}$. In the mass spectrum of this compound the heaviest ion corresponds to N-methyl-3-chloropyruvamide. Trifluoroacetic anhydride reacts with methyl isocyanide similarly to chloroacetic anhydride. Since the product of type *I* or *II* ($R^2 = \text{CF}_3$) obtained by this reaction cannot be isolated, the stoichiometry of the reaction was determined by means of the IR spectra by following the loss of the isocyanide absorption in solutions with a constant isocyanide concentration and an increasing concentration of trifluoroacetic anhydride. The results revealed that both components reacted in a ratio 1 : 1. The hydrolysis of the reaction mixture yielded a hydrated N-methyl-trifluoropyruvamide *IV*.

Tert-butyl isocyanide reacts with chloroacetic anhydride and trifluoroacetic anhydride in a ratio 2 : 1. This can be deduced from the structure of the products obtained; for the case of the reaction of trifluoroacetic anhydride it has also been verified by means of the IR spectra of the reaction mixtures. Attempts to obtain a product analogous to *II* have been unsuccessful. Hydrolysis of the reaction mixture



gave N,N'-di(tert-butyl)-O-chloroacetyl-2-chloromethyltartronamide (*V*). The IR spectrum of compound *V* contains – apart from the amide carbonyl group – also the band of the ester carbonyl group. The NMR spectrum contains two bands of the methylene groups and one band of the tert-butyl protons. The ester group of compound *V* readily undergoes aminolysis by dissolving in liquid ammonia. Chloroacetamide and N,N'-di(tert-butyl)-2-chloromethyltartronamide (*VIa*) were isolated from the reaction mixture. In the IR spectrum of compound *VIa* the ester carbonyl group is missing as expected; in the NMR spectrum there is a new signal at τ 4.95 (1 H) pertaining to the proton of the OH group, while the signal of two protons pertaining to the CH₂ group has disappeared. By reducing compound *V* with an active aluminium, one chlorine atom is replaced by a hydrogen atom. The reaction proceeds on a sterically less hindered chloromethyl group with formation of N,N'-di(tert-butyl)-O-acetyl-2-chloromethyltartronamide (*VIIa*). *VIa* is also formed by aminolysis from compound *VIIa*. However, in this case the reaction proceeds with very low yields, so that it was possible to detect the product only by thin-layer chromatography, by comparing with a sample obtained from compound *V*. Acetylation of compound *VIa* gave compound *VIIa* (whose identity was confirmed by the IR spectra). In comparison with a similar reaction of chloroacetic anhydride, the reaction of trifluoroacetic anhydride with tert-butyl isocyanide is much faster and strongly exothermal. However, during hydrolysis with water no derivative of type *V* was detected in this case, but the compound formed was directly *VIb*, in accordance with the higher reactivity of the trifluoroacetic ester. The IR and NMR spectra of this compound agree with the suggested structure. On the other hand, when the reaction mixture was decomposed with alcohol, the compound obtained had one molecule of water less than compound *VIb*. Structure *VIII* was suggested for this compound. The summary composition was verified by mass spectrometry. A molecular weight identical within the limits of experimental errors was also determined in solution, which rules out the existence of dimers or other associates under the given conditions. The IR spectrum of compound *VIII* contains in the region of the C=O and C=C bonds a strong band at 1715 cm⁻¹, somewhat weaker bands at 1815 and 1850 cm⁻¹ and a strong band at 3100–3500 cm⁻¹ corresponding to an acid hydrogen atom of the OH group. Unfortunately, it is not possible to find a direct model for the IR spectrum pertaining to 4-imino-2-azetidinone ring. Of the systems known, malonimides are the closest ones¹², having a strong band at 1725–1770 cm⁻¹ and from one to three weak bands between 1800–1900 cm⁻¹. The NMR spectrum of compound *VIII* contains only signals of the tert-butyl protons and of the proton of the OH group. All these facts, as well as the chemical reactions, agree with the suggested structure. An acid hydrolysis of compound *VIII* yields compound *VIb*. In an attempt to oxidize *VIII* with lead (IV) acetate, a small amount of the acetyl derivative *VIIIb* was isolated; this derivative has been obtained alternatively by direct acetylation of compound *VIb*.

EXPERIMENTAL

Crystallization of compounds *IV*, *Via*, *Vib*, *VIIa* and *VIII* were performed by gradually cooling solutions saturated at room temperature to -75°C . The solvents were always freshly removed from the drying agent by distillation prior to the experiment. The melting points were determined with Kofler's block and have not been corrected. The IR spectra were measured with a UR 10 apparatus in KBr pellets, if not given otherwise. The NMR spectra were measured with a JEOL-PS-100 apparatus and the mass spectra were recorded with an MS AEM 902 apparatus.

N-Chloroacetyl-N-methyl-3-chloropyruvamide (*II*)

A mixture of chloroacetic anhydride (14.6 g, 85.4 mmol) in chloroform (150 ml) and of methyl isocyanide (3.57 g, 83 mmol) in chloroform (150 ml) was left to stand at 30°C for three days. The chloroform was then evaporated, the dry residue was covered with 50 ml of ether and allowed to crystallize. The yield was 2.8 g (15%), m.p. 90°C (tetrachloromethane). A molecular ion was detected in the mass spectrum. IR spectrum: 1705 (CO—NH) and 1735 (C=O) cm^{-1} . NMR spectrum (CDCl_3): τ 6.67 (CH_3), τ 5.68 (CH_2) and 5.63 (CH_2). For $\text{C}_6\text{H}_7\text{Cl}_2\text{NO}_3$ (212.0) calculated: 33.98% C, 3.33% H, 6.60% N; found: 33.91% C, 3.39% H, 6.56% N.

N-Chloroacetyl-N-methyl-2,2-dihydroxy-3-chloropropionamide (*III*)

A solution of N-chloroacetyl-N-methyl-3-chloropyruvamide (2.2 g, 10.4 mmol) in tetrahydrofuran (10 ml) was mixed with a solution of water (0.18 g, 10 mmol) in tetrahydrofuran (5 ml). After being allowed to stand one day, the solution was evaporated to dryness and the dry residue was precipitated three times from ether with hexane. The yield was 0.25 g (9%), m.p. $110-111^{\circ}\text{C}$. IR spectrum: 1700 (C=O) and 3100—3500 (OH) cm^{-1} . The heaviest ion in the mass spectrum corresponds to N-methyl-3-chloropyruvamide. For $\text{C}_6\text{H}_9\text{Cl}_2\text{NO}_4$ (230.0) calculated: 31.32% C, 3.94% H, 30.82% Cl, 6.09% N; found: 31.68% C, 3.95% H, 29.93% Cl, 6.05% N.

N-Methyl-2,2-dihydroxy-3,3,3-trifluoropropionamide (*IV*)

A solution of trifluoroacetic anhydride (7.5 g, 35.7 mmol) in tetrachloromethane (75 ml) was added dropwise to a solution of methyl isocyanide (1.5 g, 34.9 mmol) in tetrachloromethane (15 ml). The mixture was evaporated to dryness *in vacuo*, and the dry residue was dissolved in tetrahydrofuran and decomposed with water. After evaporation *in vacuo* and crystallization from dichloromethane, 0.5 g (8%) of a compound with m.p. $110-112^{\circ}\text{C}$ was obtained. IR spectrum: 1690 (C=O) and 3100—3600 (OH) cm^{-1} . NMR spectrum (CCl_4): CH_3 band (τ 6.50) exhibits a fine structure ($J \approx 2\text{c/s}$), probably due to an interaction with the remote CF_3 group. The mass spectrum contains an ion corresponding to N-methyl-3,3,3-trifluoropyruvamide (calculated: 155.0194; found: 155.0194). For $\text{C}_4\text{H}_6\text{F}_3\text{NO}_3$ (173.1) calculated: 8.09% N; found: 8.31% N.

N,N'-Di(tert-butyl)-O-chloroacetyl-2-chloromethyltartronamide (*V*)

A mixture of chloroacetic anhydride (16.9 g, 99 mmol) in chloroform (135 ml) and of tert-butyl isocyanide (8.4 g, 101 mmol) in chloroform (85 ml) was allowed to stand at 30°C for three days, evaporated to dryness, and the dry residue was separated by extraction between 25 ml of chloroform and 10 ml of water. The aqueous layer was extracted with 2×25 ml of chloroform. The joined extracts were dried with sodium sulphate and evaporated to dryness. The dry residue was crystallized twice from tetrachloromethane. The yield, 6.2 g (35%, related to tert-butyl isocyanide), m.p. 155°C . IR spectrum 1695 (CO—NH), 1770 (C=O), 3345 and 3395 (NH) cm^{-1} . NMR spectrum (CDCl_3): τ 8.66 (two tert- C_4H_9), τ 5.78 (CH_2), τ 5.79 (CH_2). A molecular ion was detected in the mass spectrum. For $\text{C}_{14}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_4$ (355.3) calculated: 47.33% C, 6.81% H, 19.96% Cl, 7.89% N; found: 47.48% C, 6.95% H, 20.27% Cl, 7.61% N.

N,N'-Di(tert-butyl)-2-chloromethyltartronamide (VIa)

N,N'-Di(tert-butyl)-O-chloroacetyl-2-chloromethyltartronamide (1.2 g) was dissolved in an excess of anhydrous ammonia. Ammonia was removed by distillation, and the dry residue was fractionated on a silicagel column (a hundredfold excess, developed by the mixture benzene-ether 4 : 1). The first fraction was evaporated to dryness and crystallized from toluene. Yield: 0.6 g (64%), m.p. 98.5–99.5°C. IR spectrum: 1670 (CO—NH), 3330 and 3380 (NH and OH) cm^{-1} . NMR spectrum (CCl_4): τ 8.58 (two tert- C_4H_9), τ 6.32 (CH_2), τ 4.95 (OH) and τ 2.72 (two NH). A molecular ion +1 was found in the mass spectrum (calculated: 279.1476, found: 279.1458). For $\text{C}_{12}\text{H}_{23}\text{ClN}_2\text{O}_3$ (278.8) calculated: 51.69% C, 8.32% H, 12.72% Cl, 10.05% N; found: 51.89% C, 8.43% H, 12.56% Cl, 9.70% N. The second fraction contained chloroacetamide (after crystallization from dichloromethane 0.18 g; 56%). The identity with the authentic sample was checked by comparison of the respective IR spectra.

N,N'-Di(tert-butyl)-O-acetyl-2-chloromethyltartronamide (VIIa)

a) A mixture of compound V (2.1 g), tetrahydrofuran, water and activated aluminium (5 g) was allowed to react for one day; the solid phase was then removed by filtration and washed with tetrahydrofuran. The liquid portions were joined, dried with sodium sulphate and evaporated to dryness. The dry residue was crystallized from hexane. Yield 1.2 g (63%), m.p. 136°C. IR spectrum: 1685 (CO—NH), 1765 (C=O) and 3330 (NH) cm^{-1} . NMR spectrum (CCl_4): τ 8.66 (two tert- C_4H_9), τ 5.91 (CH_2) and τ 7.81 (CH_3). A molecular ion was detected in the mass spectrum (calculated: 320.1503, found: 320.1501). For $\text{C}_{14}\text{H}_{25}\text{ClN}_2\text{O}_4$ (320.8) calculated: 52.41% C, 7.86% H, 11.05% Cl, 8.73% N; found: 52.58% C, 8.07% H, 11.19% Cl, 8.72% N.

b) Compound VIa (0.35 g) was refluxed 2 h with acetic anhydride (15 ml) and pyridine (2 ml). The solution was evaporated to dryness, the dry residue was sublimated and then crystallized from hexane. Yield 0.08 g. The melting point and the IR spectrum were the same as for the product prepared sub a.

N,N'-Di(tert-butyl)-2-trifluoromethyltartronamide (VIb)

A solution of trifluoroacetic anhydride (1.3 g, 6.1 mmol) in tetrachloromethane (10 ml) was added dropwise at 0°C to a solution of tert-butyl isocyanide (1 g, 12 mmol) in tetrachloromethane (10 ml). The solution was decomposed with water, evaporated and the residue was crystallized (hexane). Yield 0.5 g (29%); the yield of the raw product was 0.9 g, m.p. 72–76°C, m.p. 78°C. IR spectrum: 1685 and 1720 (CO—NH), 3315, 3360 and 3395 (NH and OH) cm^{-1} . NMR spectrum (CCl_4): τ 8.58 (two tert- C_4H_9), τ 2.63 (two NH) and τ 4.49 (OH). A molecular ion +1 was detected in the mass spectrum (calculated: 299.1582, found: 299.1596). For $\text{C}_{12}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_3$ (298.3) calculated: 48.31% C, 7.10% H, 9.39% N; found: 48.31% C, 7.31% H, 9.26% N.

1-Tert-butyl-3-hydroxy-3-trifluoromethyl-4-tert-butylimino-2-azetidinone (VIII)

Trifluoroacetic anhydride (7.6 g, 36 mmol) in tetrachloromethane (22.5 ml) was added to a solution of tert-butyl isocyanide (5.8 g, 70 mmol) in tetrachloromethane (22.5 ml) at 0°C. The mixture was then decomposed with ethanol (15 ml), evaporated to dryness and the dry residue was crystallized from toluene. Yield 5.2 g (51%), m.p. 87°C. IR spectrum: 1715 (CO—NH), 1815 and 1850 (four-membered lactam ring) and from 3100 to 3500 (OH) cm^{-1} . NMR spectrum (CCl_4): τ 8.72 (tert- C_4H_9), τ 8.49 (tert- C_4H_9) and τ 4.00 (OH). VPO (measured with a Hitachi Perkin-Elmer, model 115 apparatus in acetone at 30°C): found 294. A molecular ion was detected in the mass spectrum. For $\text{C}_{12}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_2$ (280.3) calculated: 51.42% C, 6.83% H, 20.34% F,

10.00% N; found: 51.95% C, 7.15% H, 20.31% F, 9.91% N. Acidification of the tetrahydrofuran solution of *VIII* with a few drops of conc. hydrochloric acid yielded amide *Vib*.

N,N'-Di(tert-butyl)-O-acetyl-2-trifluoromethyltartronamide (*VIIb*)

a) A solution of 1-tert-butyl-3-hydroxy-3-trifluoromethyl-4-tert-butylimino-2-azetidinone (0.9 g) in benzene (10 ml) was refluxed three hours with an excess of lead(IV) acetate, decomposed with water, the aqueous layer was extracted with ether, the ether extract was dried with magnesium sulphate and evaporated to dryness. The dry residue was crystallized from toluene. Yield 0.2 g (20%), m.p. about 155°C (about 145°C sublimation sets in). IR spectrum: 1690 and 1730 (CO—NH), 1760 (C=O), 3290 and 3380 (NH) cm^{-1} . NMR spectrum (CD_3CN): τ 8.70 (two tert- C_4H_9), τ 7.78 (CH_3) and τ 2.20 (two NH). A molecular ion was detected in the mass spectrum. For $\text{C}_{14}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_4$ (340.3) calculated: 49.40% C, 6.81% H, 8.28% N; found: 49.60% C, 6.79% H, 8.60% N. *b*) Compound *Vib* (2.6 g) was refluxed with acetic anhydride (20 ml) and pyridine (2 ml) for three hours, the solution was evaporated to dryness, the dry residue was sublimated and twice crystallized from dichloromethane. Yield 1.7 g (57%). IR spectrum of the compound obtained is identical with the spectrum of the product described sub *a*).

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