Reaction of Cyanamide with Aryl(trichloromethyl)carbinols. A Novel Synthesis of Alkyl 5-Aryl-2-imino-4-oxo-1-imidazolidinecarboximidates

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The reaction of cyanamide with aryl(trichloromethyl)carbinols in alcoholic potassium hydroxide unexpectedly formed alkyl 5-aryl-2-imino-4-oxo-1-imidazolidinecarboximidates (**1**), in yields as high as 61%. Several reactions of these compounds are discussed. They can be hydrolyzed with acid to alkyl 1-aryl-2,4-dioxo-1-imidazolidinecarboxylates (**3**), and with base to either arylhydantoic acids or to α-aminoarylacetic acids depending upon the severity of the reaction conditions.

Aryl(trichloromethyl)carbinols are useful intermediates for the synthesis of several interesting series of compounds. Phenyl(trichloromethyl)carbinol reacts with methanolic or ethanolic potassium hydroxide to form α-alkoxyphenylacetic acids,[2] with potassium amide in liquid ammonia to form α-aminophenylacetic acid,[3] and with thiourea to form 2-imino-5-phenyl-4-thiazolidinone.[4]

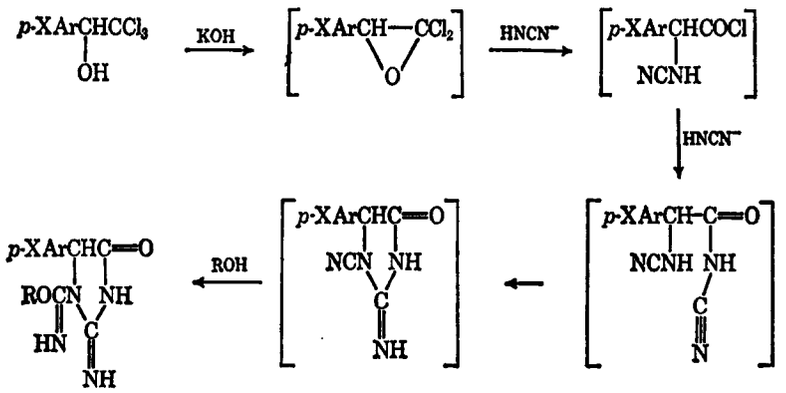
In the present work it was desired to study the reaction of various aryl(trichloromethyl) carbinols with cyanamide in alcoholic potassium hydroxide. Unexpectedly, this reaction led to a novel synthesis of alkyl 5-aryl-2-imino-4-oxo-1-imidazolidinecarboximidates (**1**), the preparation of which has not previously been described. This paper reports both the synthesis of these compounds and several of their reactions used in structural elucidation.

Synthesis.—The preferred conditions for preparing compounds **1a–f** involved adding an alcoholic potassium hydroxide solution to the aryl(trichloromethyl)carbinol and cyanamide in alcohol at 0° and finally warming the reaction mixture to 40° (Scheme I). Under these conditions, aryl(trichloromethyl)carbinols are postulated to form unstable dichloro epoxides as intermediates.[2] Accordingly, in the reaction of the aryl(trichloromethyl)carbinols with cyanamide, the cyanamide anion is believed to attack the epoxide to give first a substituted acyl chloride which in turn is attacked by a second anion of cyanamide. Subsequent cyclization and formation of an imino ether lead to the reaction product (**1**). Apparently the ring closure occurs in the strongly alkaline reaction medium, rather than during the neutralization step, because small amounts of **1** were found in the ethereal extracts of the strongly alkaline reaction mixture.

The possibility that cyanamide first dimerizes to dicyandiamide and that the latter is the intermediate which reacts with the phenyl(trichloromethyl)carbinol can be eliminated; compound **1a** is obtained in only 6% yield from the reaction of phenyl(trichloromethyl)carbinol and dicyandiamide under the usual reaction conditions.

Compounds **1a**, **1b**, and **1c** were formed in yields of 56, 61, and 28%, respectively, using ethyl alcohol as the solvent. The reduced yield with **1c** is apparently due to nucleophilic attack on the epoxide ring being inhibited by the electron-donating *p*-methoxy group. With methyl, *n*-propyl, and *n*-butyl alcohols as solvents, compounds **1d**, **1e**, and **1f** were formed in yields of 22, 38, and 38%, respectively. A competing reaction is the attack of the alkoxide ion on the postulated epoxide leading to the formation of an α-alkoxyarylacetic acid;[2] for instance, in the case of **1a** this accounted for 20% of the carbinol consumed. Potassium hydroxide in ethanol was superior to sodium ethoxide in anhydrous ethanol in spite of the fact the more anhydrous conditions are known to favor imino ether formation.

SCHEME I



1a, R = Et; X = H
b, R = Et; X = Cl
c, R = Et; X = MeO
d, R = Me; X = H
e, R = *n*-Pr; X = H
f, R = *n*-Bu; X = H

Structural Studies.—Proof of the structure assigned

(1) National Science Foundation Cooperative Graduate Fellow, 1965–1967; abstracted in part from the doctoral thesis of E. Barron, University of Maryland, 1967.

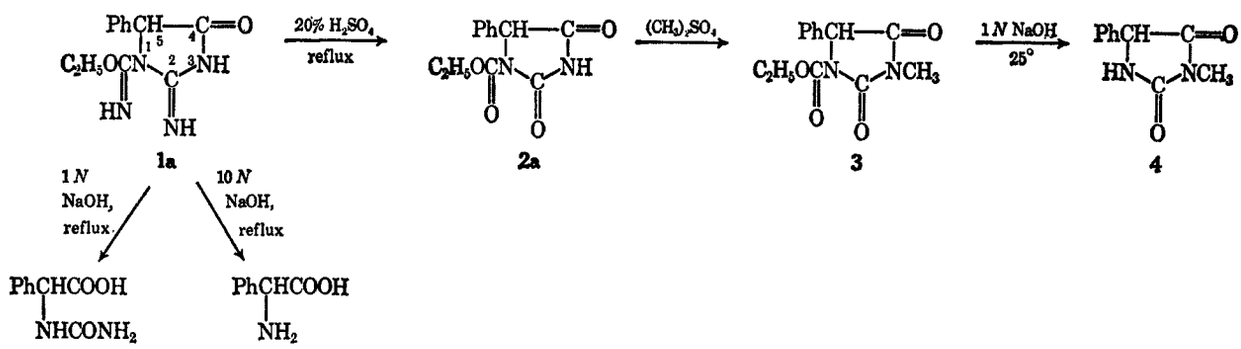
(2) Consult W. Reeve and C. W. Woods [*J. Amer. Chem. Soc.*, **82**, 4062 (1960)] for leading references.

(3) W. Reeve and L. W. Fine, *J. Org. Chem.*, **29**, 1148 (1964).

(4) W. Reeve and M. Nees, *J. Amer. Chem. Soc.*, **89**, 647 (1967).

to compound **1a** follows from analytical data (the molecular formula is $C_{12}H_{14}N_4O_2$), spectral data, certain reactions, and conversion of **1a** into a known derivative of a related compound. **1a**, only slightly soluble in common organic solvents, is soluble in dimethyl sulfoxide and in trifluoroacetic acid. The nmr spectra in these solvents clearly showed the presence of an ethyl group, the phenyl ring, the proton on carbon five, and suggested the presence of three protons on nitrogen. In trifluoroacetic acid, compound **1a** was converted into 5-phenylhydantoin. The above does not establish the position of the ethoxycarbimidoyl group. The two cyanamide moieties could add to each other to give the ethoxycarbimidoyl group substituted at either positions 1 or 3. Proof that it is in the 1 position follows from a study of compound **2a**, obtained by refluxing **1a** with 20% sulfuric acid (Scheme II). Compound **2a** is

SCHEME II



soluble in dilute base as are 1-substituted hyantoins (but not 3-substituted hydantoins), and the NH signal in the nmr spectrum (dimethyl sulfoxide solvent) occurs at δ 11.4 typical of an N–H bond at the 3 position (a proton at the 1 position gives a signal at δ 7.9–9.3).[5] Finally, methylation of compound **2a** gave an N-methyl derivative (**3**) which on hydrolysis with dilute sodium hydroxide gave the known 3-methyl-5-phenylhydantoin (**4**). Compound **1a** may also be converted into phenylhydantoic acid and into phenylglycine by refluxing with dilute and concentrated sodium hydroxide solutions, respectively.

A number of tautomeric structures are possible for compound **1**. The low solubility of this series of compounds in common organic solvents suggests a zwitterionic structure, especially since the compounds of the **2** series are readily soluble in these solvents. Furthermore, the two broad singlets occuring in the nmr spectrum around δ 9.5 and 9.0 are characteristic of a positively charged imino group.[4]

Experimental Section

All melting and boiling points are corrected. The decomposition points given, particularly for the imino carboximidates, were determined by placing the capillary melting point tubes in the melting point bath 10° below the decomposition point while the bath temperature was rising 2°/min. The ir spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Halocarbon oil mulls were used for the region 4000–1350 cm^{-1}; Nujol mulls from 1350 to 500 cm^{-1}. The nmr spectra were recorded on a Varian A-60[6] with tetramethylsilane as the internal standard; when dimethyl sulfoxide was used as the solvent, the solvent peak at δ 2.62 was used as the reference. Analyses are by Dr. Franz J. Kasler.

General Procedure for the Preparation of 1. Ethyl 2-Imino-4-oxo-5-phenyl-1-imidazolidinecarboximidate (1a).—To a stirred solution of 22.5 g (0.1 mol) of phenyl(trichloromethyl)carbinol and 10 g (0.24 mol) of cyanamide in 50 ml of absolute ethanol maintained at 1–4°, there was added over a period of 1 hr a solution prepared by dissolving 33 g of potassium hydroxide pellets in 200 ml of absolute ethanol. The reaction mixture was allowed to warm gradually to room temperature while being stirred overnight, and was then warmed to 40° for 1 hr. After the potassium chloride was filtered off and an equal volume of cold water had been added to the filtrate, the filtrate was cooled to 10° and adjusted to a pH of 7.5. The mixture was allowed to stand for 1 hr at −5°, and the precipitate was then filtered and washed with water and ethanol. The crude material melted with decomposition at 200–202° and weighed 13.6 g (56% of theory). One recrystallization from 1800 ml of 95% ethanol gave 11.4 g: mp 204–206° dec; ir 3300–3250, 3000, 1720, 1660, 1460, 1340, 1270, 1150, 1120, 1095, 890–810, 770, 750, 710, 695, and 630 cm^{-1}; nmr (DMSO) δ 9.5 and 9.0 (broad singlets, 1 and 1, N protons), 7.4 (partially split singlet, 6, C_6H_5 plus an =NH under the phenyl peak), 5.23 (s, 1, –CH<), 3.83 (q, 2, J = 7 Hz, $-OCH_2-$), 0.92 (t, 3, J = 7 Hz, $-CH_3$).

Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.67; H, 5.85; N, 22.55.

The neutral aqueous filtrate was made strongly basic and extracted with ether to remove neutral and basic material. It was then made strongly acid and extracted with ether to yield 3.8 g of crude α-ethoxyphenylacetic acid.

Methyl 2-Imino-4-oxo-5-phenyl-1-imidazolidinecarboximidate (1d).—The crude material (4 g, 22%) was recrystallized from methanol to yield 2.9 g: mp 199–200° dec; ir very similar to **1a**; nmr (DMSO) δ 9.6 and 9.0 (broad singlets, 1 and 1, N protons), 7.42 (partially split singlet, 6, C_6H_5 plus an =NH under the phenyl peak), 5.30 (s, 1, –CH<), 3.62 (s, 3, $-OCH_3$).

Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 57.06; H, 5.40; N, 23.85.

***n*-Propyl 2-Imino-4-oxo-5-phenyl-1-imidazolidinecarboximidate (1e).**—The crude material (8.8 g, 38%) melted at 197–199° dec; several recrystallizations from 95% ethanol did not alter the melting point.

Anal. Calcd for $C_{13}H_{16}N_4O_2$: C, 59.98; H, 6.20; N, 21.53. Found: C, 60.06; H, 6.32; N, 21.73.

***n*-Butyl 2-Imino-4-oxo-5-phenyl-1-imidazolidinecarboximidate (1f).**—The crude material (9.8 g, 38%) melted at 201–203° dec, unchanged after recrystallization from 95% ethanol.

Anal. Calcd for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.43. Found: C, 61.48; H, 6.65; N, 20.20.

Ethyl 5-(*p*-Chlorophenyl)-2-imino-4-oxo-1-imidazolidinecarboximidate (1b).—From 0.1 mol of *p*-chlorophenyl(trichloromethyl)-carbinol[7] there was obtained 17 g (61%, mp 183–185° dec). Three recrystallizations from ethanol raised the melting point

(5) R. A. Corral and O. O. Orazi, *Spectrochim. Acta*, **21**, 2119 (1965).

(6) We gratefully acknowledge the financial assistance of the National Science Foundation in obtaining this instrument.

(7) W. Reeve, J. P. Mutchler, and C. L. Liotta, *Can. J. Chem.*, **44**, 575 (1966).

to 191–193° dec; ir 3340, 3300, 3210, 2970, 1725, 1670, 1480, 1380, 1350, 1255, 1145, 1120, 1090, 1015, 870, 810, 755, 735, 700, 675, 660, and 590 cm^{-1}; nmr (F_3CCOOH) δ 7.55 (s, 4, ClC_6H_4–), 6.50 (broad singlet, 1, >NH), 5.92 (s, 1, –CH<), 4.49 (q, 2, J = 7 Hz, $-OCH_2-$), 1.40 (t, 3, J = 7 Hz, $-CH_3$).

Anal. Calcd for $C_{12}H_{13}ClN_4O_2$: C, 51.34; H, 4.67; N, 19.96; Cl, 12.63. Found: C, 51.40; H, 4.83; N, 19.70; Cl, 12.90.

Ethyl 2-Imino-5-(*p*-methoxyphenyl)-4-oxo-1-imidazolidinecarboximidate (1c).—From 0.5 mol of *p*-methoxyphenyl(trichloromethyl)carbinol,[7] there was obtained 38.2 g (28%, mp 180–182° dec). The product was crystallized once from 3500 ml of water, and twice from ethanol: mp 190–192° dec; ir 3255, 3000–2900, 1730, 1670, 1470, 1390, 1350, 1250, 1170, 1120, 1090, 1030, 815, 790, 750, and 680 cm^{-1}; nmr (DMSO) δ 9.4, 8.9, and 7.35 (singlets, one each, nitrogen protons), 7.14 (d, 2, J = 9 Hz, 2′ and 6′ CH of Ph), 6.91 (d, 2, J = 9 Hz, 3′ and 5′ CH of Ph), 5.12 (s, 1, –CH<), 3.92 (q, 2, J = 7 Hz, $-OCH_2-$), 3.87 (s, 3, $-OCH_3$), 1.0 (t, 3, J = 7 Hz, CCH_3).

Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.80; H, 6.10; N, 20.01.

General Procedure for the Preparation of 2. Ethyl 2,4-Dioxo-5-phenyl-1-imidazolidinecarboxylate (2a).—1a (10 g) and 100 ml of 20% sulfuric acid were heated to reflux for 1.7 hr. The reaction mixture was chilled in an ice bath and 7.2 g of the crude, white product (72%) precipitated. The precipitate, filtered off and washed with water, melts at 148–153°. One recrystallization from water gave a pure product: mp 155–157°; ir 3170, 3060, 2980, 1820, 1740, 1710, 1375, 1325, 1275, 1255, 1210, 1185, 1105, 1020, 880, 850, 790, 775, 760, 705, 655, and 560 cm^{-1}; nmr (DMSO) δ 11.4 (broad singlet, 1, –NH–), 7.36 (s, 5, C_6H_5–), 5.59 (s, 1, –CH<), 4.12 (q, 2, J = 7 Hz, $-OCH_2-$), 1.13 (t, 3, J = 7 Hz, CCH_3).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.22; H, 4.99; N, 11.00.

Methyl 2,4-Dioxo-5-phenyl-1-imidazolidinecarboxylate.—The crude material was obtained in 52% yield, mp 193–195°; after two recrystallizations from water, the melting point rose to 195–197°; ir 3170, 3070, 1805, 1740, 1450, 1395, 1310, 1285, 1165, 1120, 970, 935, 790, 760, 710, and 645 cm^{-1}; nmr (F_3CCOOH) δ 9.39 (s, 1, –NH–), 7.21 (s, 5, C_6H_5–), 5.47 (s, 1, –CH<), 3.60 (s, 3, $-OCH_3$).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.43; H, 4.50; N, 12.25.

***n*-Butyl 2,4-Dioxo-5-phenyl-1-imidazolidinecarboxylate.**—The crude material was obtained in 86% yield. Recrystallization from water gave the pure product, mp 140–142°.

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.82; H, 5.70; N, 10.24.

Ethyl 5-(*p*-Chlorophenyl)-2,4-dioxo-1-imidazolidinecarboxylate.—The crude material, mp 161–171°, was recrystallized from water to yield the pure product (54% yield): mp 178–179°; ir 3190, 3080, 1830, 1750, 1720, 1490, 1380, 1320, 1270, 1215, 1180, 1105, 1015, 880, 855, 825, 780, and 650 cm^{-1}; nmr (F_3CCOOH) δ 9.55 (s, 1, –NH–), 7.32 (s, 4, ClC_6H_4–), 5.58 (s, 1, –CH<), 4.21 (q, 2, J = 7 Hz, $-OCH_2-$), 1.12 (t, 3, J = 7 Hz, CCH_3).

Anal. Calcd for $C_{12}H_{11}ClN_2O_4$: C, 50.99; H, 3.92; Cl, 12.54; N, 9.91. Found: C, 51.27; H, 4.03; Cl, 12.80; N, 9.50.

Ethyl 5-(*p*-Methoxyphenyl)-2,4-dioxo-1-imidazolidinecarboxylate.—One recrystallization from water gave the product (66%) yield), mp 160–163°. One crystallization from water–ethanol and two more from water gave the pure product; mp 168–169°; ir 3180, 1830, 1760, 1700, 1615, 1520, 1390, 1320, 1285–1255, 1220, 1190–1170, 1100, 1020, 775, and 655 cm^{-1}; nmr (DMSO) δ 11.5 (broad singlet, 1, –NH–), 7.33 (d, 2, J = 8 Hz, 2′ and 6′ CH of Ph), 6.97 (d, 2, J = 8 Hz, 3′ and 5′ CH of Ph), 5.5 (s, 1, –CH<), 4.15 (q, 2, J = 7 Hz, $-OCH_2$), 3.78 (s, 3, $-OCH_3$), 1.05 (t, 3, J = 7 Hz, CCH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.10; H, 5.20; N, 9.93.

Ethyl 3-Methyl-2,4-dioxo-5-phenyl-1-imidazolidinecarboxylate (3).—To a mixture of compound 2a (2.2 g, 0.009 mol), 10 ml of water, and 5 ml of 2 *N* sodium hydroxide solution stirred in a beaker in an ice bath, 1.9 ml (0.016 mol) of dimethyl sulfate was added dropwise. After 45 min, the ice bath was removed, another 1.9 ml of dimethyl sulfate was added, and the mixture stirred an additional 45 min at room temperature. The mixture was chilled, and the crude produce (1.9 g) was filtered off. Recrystallization from water–methanol gave 1.6 g (70%) of needles, mp 115–116°. Several recrystallizations from water gave a purer product: mp 116–117°; ir 3060–2910, 1815, 1750, 1710, 1460, 1380, 1340, 1290, 1270, 1245, 1205, 1175, 1100, 1035, 820, 795, 770, 755, 715, and 695 cm^{-1}; nmr (DMSO) δ 7.55 (s, 5, C_6H_5–), 5.70 (s, 1, –CH<), 4.17 (q, 2, J = 7 Hz, $-OCH_2-$), 3.08 (s, 3, NCH_3), 1.12 (t, 3, J = 7 Hz, CCH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 60.09; H, 5.38; N, 10.60.

Compound 3 was converted in 69% yield into **3-methyl-5-phenylhydantoin** by stirring 0.8 g (0.003 mol) with 10 ml of 1 *N* sodium hydroxide for 1 hr at room temperature and then acidifying the solution. After recrystallizing the precipitate from water–ethanol, the material had a melting point (and a mixture melting point with an authentic sample) of 160–162° in accordance with the literature values:[8] nmr (DMSO) δ 8.60 (s, 1, –NH–), 7.42 (s, 5, C_6H_5–), 5.21 (s, 1, –CH<), 2.98 (s, 3, NCH_3).

Hydrolysis of 1a to 2-Phenylhydantoic Acid.—1a (5 g) were refluxed for 1 hr with 120 ml of 1 *N* sodium hydroxide solution, and the reaction mixture was then chilled and acidified to pH 7 so the neutral materials could be extracted with ether. The aqueous layer was then strongly acidified, chilled for several hours, and the precipitated phenylhydantoic acid (1.6 g, 42%) filtered and washed thoroughly with water: mp 177° dec (mixture melting point with an authentic sample, 178°); nmr (DMSO) δ 11.2 (broad singlet, 1, –COOH), 7.51 (s, 5, C_6H_5–), 7.02 (d, 1, J = 8 Hz, –NH–), 6.1 (broad singlet, 2, $-NH_2$), 5.40 (d, 1, J = 8 Hz, –CH<).

Hydrolysis of 1a to phenylglycine was accomplished in 56% yield by refluxing 1a with 33% sodium hydroxide solution for 7 hr. The phenylglycine obtained was identical with an authentic sample in decomposition point and ir spectrum.

Registry No.—Cyanamide, 420-04-2; 1a, 18755-65-2; 1b, 18755-66-3; 1c, 18755-67-4; 1d, 18755-68-5; 1e, 18755-69-6; 1f, 18755-70-9; 2a, 18755-71-0; methyl 2,4-dioxo-5-phenyl-1-imidazolidinecarboxylate, 18755-72-1; *n*-butyl 2,4-dioxo-5-phenyl-1-imidazolidinecarboxylate, 18755-73-2; ethyl 5-*p*-chlorophenyl-2,4-dioxo-1-imidazolidinecarboxylate, 18755-74-3; ethyl 5-*p*-methoxyphenyl-2,4-dioxo-1-imidazolidinecarboxylate, 18755-75-4; ethyl 3-methyl-2,4-dioxo-5-phenyl-1-imidazolidinecarboxylate, 18761-59-6.

(8) A. Pinner, *Ber.*, **21**, 2325 (1888); A. Kjaer, *Acta Chem. Scand.*, **4**, 899 (1950).